ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE

Ukrainian
Scientific and Practical
Peer-Reviewed Medical Journal

GENERAL SURGERY

1 | 2021

ЗАГАЛЬНА ХІРУРГІЯ

Professor Volodymyr Zemskov — a world-renowned Ukrainian surgeon

The role of choledochoscopy in transductal laparoscopic common bile duct exploration

Chronic constipation: modern view on the problem

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VIT-A-POL PUBLISHING COMPANY

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)
DOI 10.30978/GS

Bogomolets National Medical University
Національний медичний університет імені О. О. Богомольця

Ukrainian
Peer-Reviewed Scientific Specialized Medical Journal

1 | 2021

GENERAL SURGERY

ЗАГАЛЬНА ХІРУРГІЯ

Український рецензований науковий спеціалізований медичний журнал

Founded in May 2021
Quarterly journal

Заснований у травні 2021 року
Виходить 4 рази на рік

Indexed in | Журнал індексується в міжнародних наукометричних базах та каталогах
CrossRef, Vernadsky National Library of Ukraine, Google Scholar, Наукова періодика України

Kyiv | VIT-A-POL LLC | 2021

Founders
Bogomolets National Medical University
VIT-A-POL LLC

Certificate of state registration
KB No 24849-14789P granted May 7, 2021

Approved for printing by the Academic Council of Bogomolets National Medical University
Protocol No 4 signed November 25, 2021

Publishing
VIT-A-POL LLC
Office 3, 19a Academician Yefremov St., Kyiv, 03179
Tel. +38044 298-00-60. E-mail: vitapol3@gmail.com
Certificate of publishing business entity
DK No 4757 granted August 05, 2014

Project manager Bernyk O. M.
Translation and editing Holik O. V.
Design Mamchych V.

Signed for printing December 01, 2021
Circulation 1000 copies
Publishing House Avanpost-Prim LLC
3/3 Surikova St., Kyiv, 03035
Certificate of publishing business entity
DK No 1480 granted August 26, 2003

Засновники
Національний медичний університет імені О. О. Богомольця
ТОВ «ВІТ-А-ПОЛ»

Свідоцтво про державну реєстрацію
КВ № 24849-14789Р від 07.05.2021 р.

Рекомендовано Вченою радою Національного медичного університету імені О. О. Богомольця
Протокол № 4 від 25.11.2021 р.

Видавець
ТОВ «ВІТ-А-ПОЛ»
03179, м. Київ, вул. Академіка Єфремова, 19а, оф. 3
Тел. (44) 298-00-60. E-mail: vitapol3@gmail.com
Свідоцтво суб'єкта видавничої справи
ДК № 4757 від 05.08.2014 р.

Відповідальний секретар Берник О. М.
Переклад та редагування тексту Голік О. В.
Комп'ютерна верстка Мамчич В.

Підписано до друку 01.12.2021 р.
Наклад 1000 прим. Ум. др. арк. 11,16
Друк ТОВ «Видавничий будинок «Аванпост-Прим»
03035, м. Київ, вул. Сурикова, 3/3
Свідоцтво суб'єкта видавничої справи
ДК № 1480 від 26.08.2003 р.

CLINICAL CASE

КЛІНІЧНИЙ ВИПАДОК

REVIEWS

ОГЛЯДИ

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Dear colleagues!

I am delighted to introduce the first issue of a new peer-reviewed international journal — General Surgery. Our goal is to bring cutting edge surgical research and advances in clinical experience to a broad audience of the global surgical community.

The editorial board consists of a group of leading scientists from Austria, Latvia, Germany, Turkey, Ukraine, and Sweden, who have outstanding professional and academic credentials. They act as ambassadors for the new English-language journal and, among other things, strongly support the idea of promoting the Ukrainian school of surgery, its knowledge pool, achievements and strivings around the world.

Our quarterly journal will consider submissions, including, but not limited to, review articles with focus on global trends in surgical science and practice, scientific accomplishments of national surgeons, standards for diagnosis and management of surgical pathology, clinical guidelines, case reports, the latest information from scientific forums, an overview of the recent events in the field of surgery, and a history of surgical science.

The editorial board members hope for fruitful cooperation with relevant academic institutions, universities and medical institutions of the Ministry of Health of Ukraine, foreign University clinics, private clinical centers, and professional medical associations. We would like to encourage an exchange of opinions regarding the contemporary issues and further development of surgery as a part of the European research area.

I believe that our international scientific and information project «General Surgery» will be successfully realized as an unbiased source of scientific information for both national and foreign practicing and academic surgeons. Therefore, I sincerely wish success to the members of the editorial board, reviewers, authors and our publishing team in achieving this high goal.

We look forward to your contributions.

Editor-in-Chief,
Doctor of Medicine,
Professor, Head of the Department of Surgery
with a Course of Emergency and Vascular Surgery,
Bogomolets National Medical University
Yaroslav Susak

UDC 616.4-089(091)
DOI http://doi.org/10.30978/GS-2021-1-6

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Professor Volodymyr Zemskov — a world-renowned Ukrainian surgeon

The article describes the professional and scientific way of professor Volodymyr Serhiyovych Zemskov, a prominent Ukrainian surgeon and a founder of the Kyiv Center for Liver, Bile Ducts and Pancreas Surgery which is currently based in the Kyiv City Clinical Hospital No10. The article presents the memories of his students and contemporaries, the facts about his professional biography and career development. The paper describes the main scientific interests of Volodymyr Zemskov, his achievements and scientific work.

Acute pancreatitis is one of the most dangerous urgent surgical pathologies. Even at present, in the era of high-tech diagnostic equipment, methods of low-traumatic surgical interventions, availability of various pharmaceutical products, acute pancreatitis and other conditions of hepato-pancreato-biliary area contribute to high mortality among the working age population. It is considered that the surgeons, who perform upper abdominal surgeries, master the art of surgery meticulously and the specialists, who carry out urgent surgical interventions in this anatomical area must be ready to demonstrate their skills around the clock. That is, 24 hours a day and 7 days a week. Such work schedule is routine for the Kyiv Center for Liver, Bile Ducts and Pancreas Surgery which functions in the Kyiv City Clinical Hospital No10. It's difficult to count the number of lives that were saved thanks to the surgeons of the Center and the number of patients that were cured by them. The establishment of the Center became possible by virtue of one person, professor Volodymyr Zemskov, famous for his high professionalism and organizational talent. And nowadays, the functioning of this institution plays a crucial role in the health care system of the capital.

In 1982, professor Zemskov initiated the establishment of the Center at Oleksandrivska clinical hospital, one of the oldest hospitals in Kyiv. At that time, the hospital had at its own disposal 1200 beds. The Center was placed in the surgical corps which was almost 100 years old. Neither the absence of proper financial support and technical conditions nor a large flow of patients with severe urgent medical conditions didn't make professor refuse from setting up the Center. In Volodymyr Zemskov's official personal file, which is kept in the archives as the file of the official member of Kyiv medical institute, is noted that from 1982 to 1987 «*...the Center provided more than 30 000 Kyiv residents, the population of the republic as well as foreign citizens with specialized medical assistance, including surgery, hospital treatment and consultations. Professor Zemskov performs about 300 operations annually to manage the most difficult to treat conditions of the liver, biliary tract, pancreatic gland and other organs...*». In 1989, the Center was temporarily relocated to Kyiv City Clinical Hospital No10 because of the reconstruction of Oleksandrivska clinical hospital. It is, however, well known that nothing lasts longer than the temporary, so the Center functions in this medical facility even today.

Before the establishment of the Center, professor Zemskov walked a bright but thorny path in surgery. He graduated from Luhansk (at that time — Voroshilovgrad) Medical Institute in 1962. Years later, professor reminisced about his Alma Mater: «*Luhansk Medical Institute was absolutely groundbreaking with excellent teachers. There was a wide range of things*

that were allowed for us as for students: a lot of attention was focused on practice sessions, there functioned special leading-edges of all the main disciplines. I took part in the operations in the first year of medical studies. At first, of course, on dogs (by the way, since that time I've been against experiments on dogs, I like them so much). In the second or third course of my medical education I definitely knew that medicine is my way in life...». An ability to model and take part in experimental surgery influenced future professional progress of Volodymyr Zemskov. Oleksandr Shalimov discovered his talents and invited Zemskov to work for the Institute that he ran.

Before his meeting with Shalimov, Volodymyr Zemskov had worked in oncology dispensaries in Perevalne and Alchevsk for about 10 years. During that period, his working day lasted 18 hours and he performed over 100 surgical interventions including the most difficult ones.

He considered Pavlo Kravtsov, who was a surgeon and a chief of the dispensary, his first teacher-clinician. In 1969, after four unsuccessful attempts to enter the doctoral program in Moscow and Kyiv, he finally became a postgraduate student at Kyiv Research Radiological-Oncological Institute, where in a twist of fate he met Ivan Shevchenko — a leading scientist and a founder of the Institute. In 1972, Volodymyr Zemskov got his PhD degree under Ivan Shevchenko's leadership. The theme of his dissertation research was «A comprehensive diagnostics of malignant melanoma of the skin».

Then Oleksandr Shalimov noticed a talented and forward-looking PhD-surgeon. In 1973, Volodymyr Zemskov obtained a position of a junior research fellow in the department of experimental surgery. Later Volodymyr Zemskov started working at the department of liver, biliary tract and pancreatic surgery, since 1979 — as a senior researcher and a head of the department. At that time, Volodymyr Zemskov worked hard for sanitary aviation, providing special surgical assistance in the farthest outlying towns in most of the republics of the former USSR. Volodymyr Zemskov acquired valuable practical and organizational experience working under the leadership of Oleksandr Shalimov and it eventually helped him establish the Center and the Department of General Surgery of Kyiv Medical Institute. Professor Zemskov said about Oleksandr Shalimov: «I learned many things from Shalimov: in terms of both organizational qualities and the skills which are required for surgical practice and scientific activity».

In 1981, Volodymyr Zemskov obtained a Doctor of Medicine degree with the research «Surgical treatment of acute pancreatitis and its complications» and in the same year he took up the position of the chief of one of the oldest departments of Kyiv Medical Institute — the Department of General Surgery. This department was established in 1889. It developed under the leadership of such famous surgeons as Oleksandr Pavlovsky, Mykhailo Diterihs, Ivan Zavyalov and others.

Professor Zemskov knew how to reconcile surgical practice with teaching and scientific work. In 1982, he established the Kyiv Center for Liver, Bile Ducts and Pancreas Surgery where he spent most of his time.

In 1985, Volodymyr Zemskov was the first ever incumbent of Kyiv Medical Institute who received the State Prize of the USSR. He became a laureate of such an honorable award for «The development and clinical implementation of methods and techniques of cryodestruction of malignant tumours». In 1987, he was elected a member of the International Association of Hepatobiliary Surgery. In 1988, professor Zemskov received the title of the Distinguished figure of science of the USSR.

One of his most significant merits is his surgery school. During his career Volodymyr Zemskov was a teacher for many young surgeons who became professors and the heads of the department later. Today, his disciple, professor Yaroslav Susak is the head of the department of surgery with the course of emergency and vascular surgery at Bogomolets National Medical University. Professor Volodymyr Skyba is chaired by the department of surgery, anesthesiology and intensive therapy of postgraduate education at the same university. Professor Vasyl Khrapach leads the department of plastic and reconstructive surgery of postgraduate education at Bogomolets National Medical University.

«There are surgeons who can operate perfectly, create a school to teach doctors and capture them with their ideas and lead people. This is exactly about my teacher Volodymyr Zemskov...» — that's how surgeon Yuryi Lifshyts said about his teacher and added: «He belongs to those people who work pushing themselves to the limit. His manner of life was very close to Vysotskyi. He read a lot, he knew everything. A high intelligence. Shalimov developed and realized the most difficult researches with Zemskov. For example, treatment of purulent pancreatitis. The mortality caused by this condition in 1970s was about 70%. Zemskov implemented a technique which allowed to reduce it and defended his doctoral dissertation. He looked after literally every patient after the operation by himself».

Professor Zemskov, despite his status, personally participated in the rehabilitation of his patients. He was an extremely sensitive doctor. Not only a surgeon, but also a psychologist for his patients. Volodymyr Zemskov said: «*Unfortunately, death is*

In the center — Volodymyr Zemskov, mid-1970s

inevitable, no matter how hard you fight it. But it's scary when there is an opportunity to save a person, and it is not used because of someone's stupidity and laziness. This is a big sin. Sometimes, according to all prognoses, a person must die, and they still survive. Or vice versa: the operation was successful, the wounds heal quickly, but the disease suddenly progresses again. I believe that recovery depends on both the psychological state and the soul, the presence of the spiritual in a person, something that we cannot fully understand...».

Of course, this pace and intensity of work influenced Professor Zemskov. He finds relief from chronic fatigue and regular stress at home, with his family. Professor Zemskov greatly appreciated the time he spent with his beloved wife and children who also became doctors in the future. «Family and home are extremely important. My wife is also a doctor, we met at the institute, it was love at first sight. We have been together for more than 30 years since then. When you come after a hard shift, after many hours of operations, it is just necessary that the family supports you, listens, understands... "- the professor said to his students.

In 1995, Volodymyr Zemskov was awarded the title of Academician of the Universal Academy Guglielmo Marconi (Rome, Italy) for his medical research in the field of cancer. He was elected a member of the European Order of Dignity A. S. O. E. M. (Brussels, Belgium) and the Albert Schweizer Society (Austria), as well as many other international charitable non-profit organizations. In 1997, he was elected a member of the International Surgical Society (ISS).

During the 90s, the professor continued to run the department and the Center. He began to develop the newest, at that time, direction — endovideoscopic surgery and to introduce it into the practice of treatment of acute surgical diseases of the hepato-pancreato-biliary zone. He continued to spend most of his time at work and in the best traditions of medical self-sacrificing humanism «burned himself while shining a bright light on others». One of his numerous students, Professor Inna Kovalska, recalled: *«Even if other doctors abandoned the patient, believing that it was impossible to save him, Zemskov operated. Here is a vivid example: a 16-year-old girl who was diagnosed with a malignant tumor of the pancreas which was estimated as inoperable by the different surgeons, but Volodymyr Zemskov removed her tumor and prescribed a course of treatment. The girl survived. The professor always said: «It is not for us to judge how many days, months, years a person is allowed, the task of a doctor is to make this time not a continuous torment, but a real life...».*

During his life, Professor Zemskov was the author of more than 500 scientific papers, 5 monographs, 45 inventions and patents.

In 2002, a year before the 30th anniversary as the head of the Department of General Surgery, Volodymyr Zemskov died of myocardial infarction at the age of 61. In 2009, a granite memorial plaque, commemorating Volodymyr Zemskov, was erected at the surgical building of the Kyiv City Clinical Hospital No10, where the Center established by the professor continues to function. His name is forever engraved in the history of national surgery.

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Професор Володимир Земсков — всесвітньовідомий український хірург

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У статті представлено професійний та науковий шлях професора Володимира Сергійовича Земскова — видатного українського хірурга, засновника Київського центру хірургії печінки, жовчовивідних шляхів та підшлункової залози, який сьогодні функціонує на базі Київської міської клінічної лікарні № 10. Наведено спогади учнів та сучасників, факти щодо професійної біографії та кар'єрного становлення. Також описано основні наукові інтереси Володимира Земскова, його здобутки та наукові роботи.

UDC 616.367-003.7-089.832
DOI http://doi.org/10.30978/GS-2021-1-10

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

The role of choledochoscopy in transductal laparoscopic common bile duct exploration

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Laparoscopic common bile duct exploration (LCBDE) performed by choledochoscope through the cystic duct or directly through the incision in the common bile duct (CBD) are well established methods for restoring biliary drainage function in patients with choledocholithiasis. Although it plays a crucial role in the transcystic approach, transductal approach can be achieved differently. However, it has restrictions in availability due to its expensiveness.

Objective — to report efficacy of transductal LCBDE without laparoscopic choledochoscopy.

Materials and methods. This is a prospective study of urgently admitted patients who underwent trans-ductal LCBDE due to confirmed choledocholithiasis. During laparoscopy, clearance of the CBD was achieved in two ways: by choledochoscopy (group CS+, n=43) and without it (group CS–, n=34). The data of patient demographics, comorbidities, operative outcomes, morbidity, mortality and long-term biliary complications were analysed and compared between the groups.

Results. Out of a total of 154 patients with confirmed choledocholithiasis, the trans-ductal approach of LCBDE was applied to 77 patients. In 43 patients, clearance was done with choledochoscope (group CS+) and in 34 patients without it (group CS–). Gallstone related complications and comorbidities did not differ between the groups. Surgery was done 4 days after admission in both groups. Median duration of the operation was significantly shorter in the group CS–, 93 vs 120 minutes (p=0.036), without any difference in conversion and complication rates. Clearance rate was markedly high in both groups.

Conclusions. Transductal laparoscopic common bile duct exploration without choledochoscopy is a time-saving, safe and effective way for CBD clearance, without additional equipment.

Keywords
choledocholithiasis, laparoscopic common bile duct exploration, intraoperative ultrasound, choledochoscopy.

ARTICLE • Received 2021-11-11 • Received in revised form 2021-11-17

Gallstone related complications resulting from choledocholithiasis are associated with potentially life-threatening conditions such as biliary pancreatitis and cholangitis often accompanied by mechanical jaundice that requires urgent restoration of biliary drainage function. Recently reported studies have shown incidence of the common bile duct (CBD) stones up to 8—20 % in patients with gallstone disease [1]. Existing recommendations suggest two main approaches to the treatment of these conditions — endoscopy first or a one-step surgery.

Endoscopic retrograde cholangio-pancreatography (ERCP) is widely accepted and can be a useful procedure for the treatment of choledocholithiasis [2]. However, the method is invasive and associated with a 5—10 % complication rate and 0.1—1 % mortality rate [3]. Along with the progressive course of advanced laparoscopy, laparoscopic common bile duct exploration (LCBDE) assisted by laparoscopic choledochoscopy has become an effective and safe alternative [4] as well as more advantageous in comparison with a two-step approach [5]. However, choledochoscopy has restrictions due to its expensiveness and availability.

Despite the fact of consensus on the transcystic choledochoscopy in patients with small stones and

not dilated CBD, there is still undefined technique for LCBDE for transductal approach and the role of choledochoscopy in it.

Objective — to report efficacy of transductal LCBDE without laparoscopic choledochoscopy.

Materials and methods

Patients

This clinical study includes urgently admitted and prospectively collected patients during the time period from January 2012 to February 2016 with complicated gallstone disease and high risk of choledocholithiasis according to the criteria of the American Society of Gastrointestinal Endoscopy [13] (Fig. 1). All patients were selected for laparoscopic cholecystectomy and common bile duct exploration in a single time. Patients with transcystic approach were excluded from the study, whereas patients with transductal approach were further analysed and stratified in two groups according to the way of CBD clearance — with (group CS+) or without choledochoscopy (group CS–) (Fig. 2). Complicated forms of gallstone disease were based on evidence of biliary pancreatitis, cholangitis and/or characteristic symptoms complex of biliary colic frequently accompanied by pale stools and dark urine. Preoperative diagnosis of cholangitis was based on the criteria recommended in the Tokyo Guidelines 2013 — evidence of inflammatory response (increased white blood cells > $10 \cdot 1000/\mu L$) or CRP > 10 mg/L, cholestatic pattern presented by abnormal liver function tests (alkaline phosphatase, GGT, ALT, AST ≥ 1.5 standard deviation) or bilirubin ≥ 34.2 μmol/L and gallstones in the gallbladder and/or dilatation of the common bile duct > 6 mm confirmed by trans-abdominal US [9, 10]. The diagnosis of biliary pancreatitis was made when two of the following revised Atlanta 2012 criteria were presented — abdominal pain consistent with acute pancreatitis; serum lipase activity more than three times greater than the upper limit of normal; and characteristic findings of acute pancreatitis on radiological investigations [11]. Severity grading of cholangitis and pancreatitis were also evaluated according to the Tokyo Guidelines 2013 (Fig. 3) and revised Atlanta 2012 criteria (Fig. 4), respectively. Preoperative anesthesiological status was assessed in all patients using the American Society of Anaesthesiologists Physical Status classification system (ASA score) [6, 7].

Predictors of choledocholithiasis

- Very strong
  - CBD stone on transabdominal US
  - Clinical ascending cholangitis
  - Bilirubin > 4 mg/dL
- Strong
  - Dilated CBD on US (> 6 mm with gallbladder *in situ*)
  - Bilirubin level 1.8—4.0 mg/dL
- Moderate
  - Abnormal liver biochemical test other than bilirubin
  - Age older than 55 years
  - Clinical gallstone pancreatitis

Assigning a likelihood of choledocholithiasis based on clinical predictors

Presence of any very strong predictor	*High*
Presence of both strong predictors	*High*
No predictors present	*Low*
All other patients	*Intermediate*

Figure 1. **Predictors of choledocholithiasis (American Society of Gastrointestinal Endoscopy)**

Diagnosis of choledocholithiasis

In the time of admission all patients had transabdominal ultrasound (TAUS) investigation as a screening where indirect signs of the presence or absence of CBD stones, specifically the CBD diameter more than 6 mm or intrahepatic bile duct dilation, were evaluated. According to the availability, part of them had preoperative magnetic resonance cholagio-pancreatography (MRCP) or computed tomography (CT) in case of suspected malignancy. During laparoscopy all patients underwent intraoperative ultrasound (IOUS) for approval of previously detected or diagnosing choledocholithiasis.

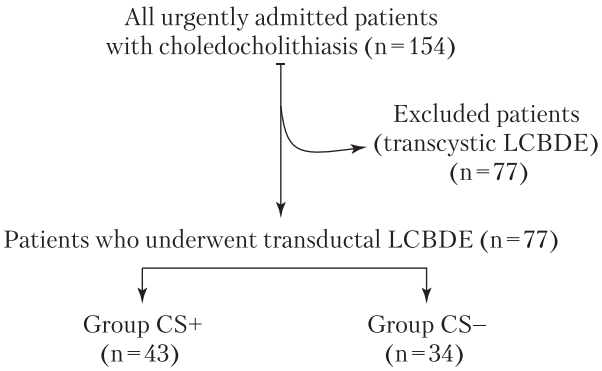

Figure 2. **Study population**

Grade I (mild) acute cholangitis
Grade I cholangitis does not meet the criteria of Grade III (severe) or Grade II (moderate) acute cholangitis at initial diagnosis

Grade II (moderate) acute cholangitis
Grade II acute cholangitis is associated with any two of the following conditions:
- Abnormal white blood cells count ($> 12{,}000$ mm^3, $< 4{,}000$ mm^3)
- High fever (≥ 39 °C)
- Age (≥ 75 years old)
- Hyperbilirubinemia (total bilirubin ≥ 5 mg/dL)
- Hypoalbuminemia ($<$ standard deviation $\cdot$ 0.7)

Grade III (severe) acute cholangitis
Grade III acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the following organs/systems:

Disfunctions	**Parameters**
Cardiovascular	Hypotension required dopamine ≥ 5μg/kg per min, or any dose of epinephrine
Neurological	Disturbance of consciousness
Respiratory	PaO_2/FiO_2 ratio < 300
Renal	Oliguria, serum creatinine > 2.0 mg/dL
Hepatic	International normalised ratio > 1.5
Hematological	Platelet count $< 100{,}000$ mm^3

Figure 3. **Severity grading of cholangitis (Tokyo Guidelines 2013)**

Mild acute pancreatitis	No organ failure; no local and systemic complications
Moderate acute pancreatitis	Transient organ failure (< 48 hours) and/or local or systemic complications or exacerbation of pre-existing comorbidities
Severe acute pancreatitis	Persistent organ failure (single or multiple)

Figure 4. **Severity grading of pancreatitis (revised Atlanta criteria 2012)**

Laparoscopy

The standard four-trocar technique was used for cholecystectomy and LCBDE. At the beginning of operation, Callot's triangle was dissected and cystic duct, artery and common bile duct were identified. Cystic duct and artery were clipped and cystic artery was divided. The gallbladder was left *in situ* and retracted during IOUS and LCBDE.

IOUS was performed with BK Medical flex Focus 800 US machine and special flexible laparoscopic transducer 8666-RF. The US transducer was inserted through the epigastric trocar and placed on the superior edge of the hepatoduodenal ligament and slid inferiorly to the distal end for the examination of CBD. The proximal part of CBD, left and right hepatic ducts and their junction were investigated through the right hepatic lobe. Diameter of CBD and cystic duct, as well as the size and number of stones were measured for determining the approach of choledochoscopy. The transcholedochal approach was chosen in cases when stones in CBD were larger than the obtainable diameter of cystic duct or when very distal insertion of the cystic duct in CBD was found by IOUS, or when common bile duct was more than 10 mm and choledocho-duodenostomy was expected, or when more than five stones were found.

An incision of the supraduodenal part of CBD was made longitudinally and the duct was flushed with normal saline. Afterwards, in group CS+, 2.5 mm flexible choledochoscope was inserted in a distal as well as in a proximal part of the bile duct and lobar intrahepatic bile ducts were examined. The stones were removed using Dormia baskets inserted through the instrument channel of the choledochoscope. However, in the group CS– clearance of CBD was achieved using Fogarty (No 3 or 4) catheters or extensive flushing with saline. After removal of all stones, clearance of the common bile duct was confirmed with repeated IOUS. After clearance common bile duct was closed in three ways: primary closure with interrupted 3—0 absorbable sutures and in exceptional cases of severe cholangitis or CBD > 15 mm, T-tubes or choledocho-duodenostomies were performed.

All IOUSs and LCBDEs were performed by specially trained surgeons.

The data of patient demographics, comorbidities, operative outcomes, morbidity, mortality and long-term biliary complications were analysed and compared between the groups.

Statistical analysis

The interval data was presented in median (Me) with interquartile range (IQR) and was confirmed by the Kolmogorov-Smirnov test for the asymmetrical distribution of data. Comparison of the interval

data in groups CS+ and CS– was performed with the Mann-Whitney U test, the nominal data comparison was performed using the Pearson χ^2 test and Fisher's exact test. Significant dynamics of laboratory analysis were revealed by the Wilcoxon test. The correlation between hospital stays and clinical data was evaluated using the Spearman rho method. Also, the correlation coefficient was compared between the groups. A logistic regression analysis was performed to identify factors associated with a longer hospital stay. A p-value < 0.05 was considered as statistically significant. The statistical analysis was performed with SPSS version 20 and MedCalc version 15.

Results

Demographics

Out of a total of 154 patients who were urgently admitted and had confirmed stones in the common bile duct, 77 underwent transductal LCBDE (see Fig. 1). From this cohort, transductal LCBDE was done by laparoscopic choledochoscope in 43 patients (group CS+) and without it in 34 patients (group CS–). There were 22 males and 55 females in the cohort. The median age in cohort was 65 years (IQR 74.5—55.5) and that did not differ between the groups as well as there was no obvious statistically significant difference in gender and comorbidities (according to the ASA score). Biliary pancreatitis was more evident in the group CS– (p = 0.028), however, cholangitis in the group CS+ (p = 0.028). Patients with jaundice were presented equally in both groups. The median preparation time for patients before surgery was equally 4 days in the groups (IQR 6—2) (Table 1).

Preoperative radiological imaging study

Pre-operative screening performed by trans-abdominal US was done in 71 patients of cohort and CBD stones were found in 28—48 % of patients without difference in the groups. Specific preoperative diagnostic modalities like CECT and MRCP were done in 27 patients of cohort (35 %) without difference between the groups. Choledocholithiasis was established in 40—67 % of patients examined by CECT, and in 80—89 % of patients examined by MRCP (Table 2).

Laparoscopy

The median time of surgery was statistically significantly shorter in the group CS– without considerable rate of conversions. There were two patients in the group CS+ with conversion to open surgery due to the impacted stones in CBD. IOUS was done successfully in all patients. Larger stones in CBD as well as more pronounced dilation of CBD were detected significantly frequently in the group CS–.

Choledocho-duodenostomies were performed significantly more often in the group CS–, mostly due to the excessive (over 15 mm in diameter) dilatation of CBD and objective signs of papillary stenosis (unsuccessful insertion of 3 mm drain through the papilla). However, T-tubes were placed in 17 patients of all cohort, mainly due to the cholangitis, without difference between groups. Primary closure was achieved in 61 % of the group CS+, which is significantly more often compared with the group CS– (Table 3).

Table 1. **Preoperative characteristics**

Indicator	CS+ (n = 43)	CS– (n = 34)	p
Age, years	62 (74—47)	68 (76—62)	0.087
Male/female	13/30	9/25	0.717
Pre-operative time, days	4 (6—2)	4 (6—2)	1
ASA I	8	6	0.936
ASA II	21	18	0.936
ASA III	14	10	0.936
Concomitant pancreatitis	6	12	0.028
Mild	3	0	0.099
Moderate	1	2	0.099
Severe	2	0	0.099
Cholangitis	33	18	0.028
Mild	25	8	0.031
Moderate	8	8	0.031
Severe	0	2	0.031
Jaundice	29	22	0.801

Quantitative data are presented as mean (interquartile range), categorial data are presented as a number of cases.
ASA — American Society of Anaesthesiologists Physical Status classification system.

Table 2. **Preoperative radiological imaging study**

Indicator	CS+ (n = 43)	CS– (n = 34)	p
TAUS	11 (28.0 %)/40	15 (48.0 %)/31	0.070/1
CECT	2 (40.0 %)/5	2 (67.0 %)/3	0.155/1
MRCP	8 (89.0 %)/10	8 (80.0 %)/9	1/0.745

The data are presented as verified choledocholithiasis/total number of patients studied.
TAUS — trans-abdominal ultrasound;
MRCP — magnetic resonance cholangiopancreatography;
CECT — contrast-enhanced computed tomography.

Complication rate

The overall postoperative complication rate was observed in 11.7 %, including mild pancreatitis in two patients from the group CS+, treated conservatively, as well as a bile leak in one patient, which was conservatively treated for 3 days by drainage, one bleeding from the liver bed with obtained hemostasis by re-laparoscopy, one subhepatic biloma drained percutaneously with ultrasound guidance, one case with retained stone in CBD underwent successful endoscopic clearance and one patient with embolism of pulmonary artery. However, in the group CS–, one patient developed hypertension crisis that was averted by medications, and one patient had a bile leak from choledocho-duodenostomie and bile peritonitis. Despite the re-operation and repair of anastomosis, the above-mentioned case resulted in irreversible multiorgan disfunction and death.

Table 3. **Operation data**

Indicator	CS+ (n = 43)	CS– (n = 34)	p
Operation time, min	120 (140—90)	93 (125—76)	0.036
Diameter of CBD, mm	12 (15—10)	18 (20—13)	0.001
Largest stone in the CBD, mm	8 (10—6)	10 (15—10)	< 0.001
Primary closure	26 (61.0 %)	5 (15.0 %)	< 0.001
T-tubes	10 (23.0 %)	7 (21.0 %)	0.779
Choledocho-duodenostomies	7 (16.0 %)	22 (65.0 %)	< 0.001
Conversion of laparoscopic to open surgery	2 (5.0 %)	0	0.502

Quantitative data are presented as mean (interquartile range), categorial data are presented as a number of cases and percentage.

Table 4. **Main outcomes**

Indicator	CS+ (n = 43)	CS– (n = 34)	p
Hospital stay, days	12 (16—9)	11 (13—8)	0.428
Post-operative time, days	6 (10—4)	6 (8—5)	0.756
ICU stay, days	6 (14.0 %)	7 (21.0 %)	0.440
Morbidity	7 (16.2 %)	2 (5.8 %)	0.097
Mortality	0	1 (3.0 %)	0.442
Readmission	5 (12.0 %)	3 (9.0 %)	1
Clearance rate of CBD, %	95	100	0.189

Quantitative data are presented as mean (interquartile range), categorial data are presented as a number of cases and percentage.

Outcomes

Postoperative and total hospital stay was not significantly different in the groups. Totally 13 patients in postoperative period were treated in ICU without difference in the number of patients and days between the groups. One year readmission rate due to late biliary complications was similar. The reasons for re-hospitalization included choledocholithiasis, acute pancreatitis, cholangitis, whereas one patient was re-hospitalized to evacuate choledochostome. Choledocholithiasis was successfully managed with ERCP. Totally complete clearance rate of the common bile duct was high, without difference in the groups (Table 4).

Correlation analysis

Correlation analysis revealed that the total hospital stay had a moderate positive correlation in patients with inserted T-tubes and a strong positive correlation with severity of biliary pancreatitis in groups CS+ and CS–. However, choledocho-duodenostomies in the group CS– patients was associated with less hospital stay. Prolongation of total hospital stay was associated with comorbidities according to ASA score in the group CS+.

Discussion

Consensus exists that the therapy for choledocholithiasis should be administered with the fewest number of procedures, lowest cost and less morbidity. Considering the fact that the recent study reported 11 %-21 % high incidence of choledocholithiasis in patients with gallstone disease at the time of cholecystectomy [13] and the variety of different modalities for CBD stones managing, there is still no consensus concerning the management of CBD stones. In general, there are two different approaches recommended in the literature for management of choledocholithiasis, based on more accurate preoperative diagnosis followed by endoscopic procedure and delayed surgery or definitive treatment of choledocholithiasis during laparoscopic cholecystectomy without specific pre-operative radiological investigation.

Magnetic resonance cholangio-pancreatography is considered as a routine, specific preoperative non-invasive diagnostic modality for the biliary tree, with a high sensitivity (81—100 %) and specificity (92—100 %) [21]. However, MRCP may miss

the stones less than 5 millimetres in diameter and bile sludge especially in the case of pancreatitis [22—24]. Moreover, there are some medical restrictions in MRCP, like expressed obesity, claustrophobia, and metallic prostheses.

Endoscopic retrograde cholangio-pancreatography (ERCP) usually combined with endoscopic papillotomy is a widely used treatment tool for patients with a high risk of biliary stones [13—15]. Despite the fact of high sensitivity (89 %–93 %) and specificity (100 %) [15], the complications associated with ERCP are remarkable. Relatively high incidence of post-ERCP pancreatitis in general population is still a problem and it occurs in 4.5 % [16—18]. Other complications like bleeding, perforation of duodenum or bile duct and post-papillotomy ascending cholangitis and cholecystitis can occur in 5 %– 8 %, as well as mortality due to this procedure in 0.2—0.5 % [19, 20]. Even more, ERCP may fail in case of difficult anatomy, biliary strictures or large stones (more than 10—15 mm in diameter or equal to the CBD diameter) even if performed by experienced endoscopists [27].

Considering the requirement of more advanced skills in laparoscopic surgery and choledochoscopy, ERCP still remains the first method of choice in many hospitals, but recently published articles demonstrated similar or better clearance rate of biliary stones performed by LCBDE compared to a two-step approach, as well as the complications related with papillotomy like cholangitis can be avoided [28, 29]. Moreover, contrary to the view that ERCP alone is used more often in elderly patients with significant comorbidities, LCBDE can be safe for elderly patients with undifferentiated results in general population [30]. Most authors suggest common bile duct exploration simultaneously with laparoscopic cholecystectomy [23—26].

LCBDE is performed either by the application of trans-cystic or trans-ductal approaches, and the role of choledochoscopy is paramount. Trans-cystic approach of choledochoscopy is restricted in many patients because of the limited size of the stones (< 6 mm), number of the stones (< 5) and size of the cystic duct [31, 33]. Moreover, transcystic stone clearance may be hampered by anomalous anatomy, proximal (common hepatic duct) stones and biliary strictures [41]. If the patients are not suitable for these criteria, the trans-ductal approach should be applied. Despite the advantages of LCBDE, it is associated with a higher risk of bile leakage, especially for the trans-ductal approach, [32] and should be performed by highly experienced and skilled surgeons. However, many limitations for the use of choledochoscopy still exist. Most of choledochoscopes are guided in two planes which restricts manoeuvring as well as two trained surgeons are required for the procedure [34]. Moreover, application of the choledochoscopy is associated with lack of availability and prolonged learning curve.

The results of our study confirmed the findings reported in the literature that the patients' general status, comorbidities and typical complications (bile leakage, bleeding from the liver bed) were similar in patients who underwent LCBDE. Pre-operative radiology by TAUS screening was mostly ordered for detecting indirect signs suggestive of the possibility of the CBD stones. However, pre-operative CECT scan and MRCP were performed when other reasons of bile stasis (mostly malignancy) were suspected [21, 35, 36].

The above-mentioned results demonstrate that choledochoscopy significantly increases duration of surgery compared with the group CS– as well as conversions were not observed in the group CS–. For the clearance control after CBD exploration as well as for diagnosis of choledocholithiasis before exploration we used IOUS. IOUS is a useful, safe, non-invasive, quick imaging method with a sensitivity and specificity of 80 %-100 % and 98 %-100 %, respectively [37—39]. It can be repeated in any time of surgery. Moreover, IOUS is useful in cases with severe infiltrate and difficult anatomy. High clearance and low readmission rate due to residual stones in CBD prove efficacy of this method [40], similarly to our study.

Additional T-tubes were used similarly in both groups in patients with a significant risk of bile leakage from choledochotomy (severe cholangitis, uncertainty regarding duct clearance, edema or spasm of the sphincter after exploration), like it is reported in other studies (41) and in any case T-tubes as a controlled biliary fistula allow postoperative radiological evaluation of the biliary system for retained stones and early endoscopic clearance when indicated. However, choledocho-duodenostomies were performed in selected cases, significantly more often in the group CS– due to the extensive dilatation of CBD. Primary closure of CBD after clearance was achieved in cases that lacked the abovementioned conditions, significantly more often in the group CS+. The similar recommendations and results for primary closure of CBD were reported by other authors [42, 43].

According to the results of our study and reported studies, the hospital stay is strongly associated with a use of T-tubes [42, 43] and severity of biliary pancreatitis. Similarly to the reported data, comorbidities based on ASA score were associated with a prolongation of hospital stay [44].

This study shows that LCBDE guided by intraoperative ultrasonoscopy in transductal approach without choledochoscope resulted in high clearance rate, low complication rate and low one-year readmission rate.

Conclusions

Transductal laparoscopic common bile duct exploration without choledochoscopy is a time-saving, safe and effective way for bile duct cleaning without additional equipment.

Declaration of interests

Authors have no conflict of interest to declare.

Ethics approval and written informed consents statements

The assessment and usage of all clinical data was approved and permitted before the study by the ethics committee of the Riga Stradins University. The study protocol conformed to the ethical guidelines of the «World Medical Association (WMA) Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects» adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008 [8].

Author contributions

K. Atstupens: conception and design, acquisition, analysis and interpretation of data, drafting the article, critical revision of the article; H. Plaudis: conception and design, critical revision of the article; E. Saukane, A. Rudzats: acquisition, analysis and interpretation of data.

All authors have read and agreed to the published version of the manuscript.

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Роль холедохоскопії при черезпротоковому лапароскопічному дослідженні загальної жовчної протоки

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Лапароскопічне дослідження (ЛД) загальної жовчної протоки (ЗЖП), яке виконують холедохоскопом крізь міхурову протоку або безпосередньо шляхом розсічення ЗЖП, є поширеним методом відновлення функції пасажу жовчі у пацієнтів з холедохолітіазом. Хоча цей метод відіграє вирішальну роль при черезміхуровому доступі, останній може бути виконаний різними способами. Однак через високу вартість цей метод не часто застосовують.

Мета — повідомити про ефективність черезпротокового лапароскопічного дослідження загальної жовчної протоки без лапароскопічної холедохоскопії.

Матеріали та методи. Проведено проспективне дослідження 77 терміново госпіталізованих пацієнтів, яким виконали черезпротокове ЛД ЗЖП з приводу підтвердженого холедохолітіазу. Під час лапароскопії видалення конкрементів ЗЖП проводили двома способами: з використанням холедохоскопії (група CS+, n=43) та без неї (група CS–, n=34). У групах дослідження порівняно демографічні показники, характер та частоту супутніх захворювань, результати операцій та летальність.

Результати. За ускладненнями та супутніми захворюваннями, пов'язаними з жовчнокам'яною хворобою, групи не відрізнялися. Операцію проводили через 4 дні після госпіталізації в обох групах. Медіана тривалості операції була статистично значущо (p=0,036) меншою в групі CS– (93 та 120 хв відповідно). Не виявлено різниці за частотою конверсії та ускладнень. Кліренс був істотно високим в обох групах.

Висновки. Черезпротокове ЛД ЗПЖ без холедохоскопії — це економний, безпечний та ефективний спосіб видалення конкрементів ЗЖП без додаткового обладнання.

Ключові слова: холедохолітіаз, лапароскопічне дослідження загальної жовчної протоки, інтраопераційне ультразвукове дослідження, холедохоскопія.

FOR CITATION

Atstupens K, Plaudis H, Saukane E, Rudzats A. The role of choledochoscopy in transductal laparoscopic common bile duct exploration. General Surgery (Ukraine). 2021:1;10-17. http://doi.org/10.30978/GS-2021-1-10.

UDC 616-008.9-056.257-089.834
DOI http://doi.org/10.30978/GS-2021-1-18

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

The role of endoluminal interventions in the preparation of high-risk patients with super-obesity for bariatric surgery

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Obesity causes increased morbidity, disability and mortality rates as well as affects the quality of life. Given the known risks to the patient's health, the International Federation for the Surgery of Obesity and Metabolic Disorders pays special attention to the problem of morbid obesity (body mass index ≥ 40 kg/m^2), with particular emphasis on super-obesity (body mass index ≥ 50 kg/m^2).

Objective is to investigate the role of endoluminal interventions in the preparation of super obese patients with high risk of surgical and anaesthesia-related complications for bariatric surgery.

Materials and methods. From 2011 to 2018, 97 patients with morbid obesity and high risk of surgery and anaesthesia-related complications (ASA PS III—IV) underwent a course of treatment at the clinical setting of the Department of General Surgery No2 of Bohomolets National Medical University. The treatment was carried out in 2 stages. In the main group (n = 60), the first stage of treatment included the intragastric balloon placement for a term of 6 months. The control group (n = 37) received a six-month conservative therapy. In the second stage of treatment the patients of both groups underwent a surgical procedure for the morbid obesity management.

Results. The outcomes of the first stage of treatment showed that the patients, who underwent the intragastric balloon placement, had statistically significantly ($p < 0.001$) higher mean the percentage of excess weight loss (%EWL) than the patients who received conservative therapy. In the main group, the average ASA PS score, which is identified as an anaesthetic and surgical risk indicator, decreased from 3.28 (95 % confidence interval (CI) 3.17—3.40) to 2.15 (95 % CI 2.06—2.24, $p < 0.001$), and in the control group — from 3.24 (95 % CI 3.10—3.39) to 3.14 (95 % CI 2.96—3.31, $p > 0.05$).

Conclusions. The results of the study provide strong evidence that the intragastric balloon placement for a term of 6 months reduces surgical and anaesthetic risks, contributes to the improved function of the cardiovascular and respiratory systems as well as gives a boost to carbohydrate metabolism, and, therefore, can be suggested for the preparation of super obese patients with high risk of surgical and anaesthesia-related complications for bariatric surgery.

Keywords
morbid obesity, bariatric surgery, type 2 diabetes mellitus.

ARTICLE • Received 2021-10-18 • Received in revised form 2021-10-20

Obesity is an urgent health problem as its social and health impact is extremely high today. Around 13 % of adults worldwide are suffering from obesity. According to the global health estimates, by 2025 about 20 % of the world population will be diagnosed with obesity [9]. Obesity causes increased morbidity, disability and mortality rates as well as affects the quality of life [7]. Given the known risks to the patient's health, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) pays special attention to the problem of morbid obesity (body mass index (BMI) ≥ 40 kg/m^2), with particular emphasis on super-obesity (BMI ≥ 50 kg/m^2) [12].

The inadequate effectiveness of conservative methods of treatment necessitates the application of bariatric surgery [3, 8]. However, these patients have a high surgical and anaesthetic risk, including in terms of anaesthesia administration. Particularly serious problems result from the complications of pulmonary embolism, which are presented in a 24-year retrospective analysis of bariatric interventions [11]. In general, postoperative mortality in obese patients is 2 times higher than in people with normal body weight [10].

E.J. DeMaria et al. (2007) propose the OSMRS (The Obesity Surgery Mortality Risk Score) scale, which is based on five preoperative variables that increase the risk of morbidity and mortality within 30 days after gastric bypass. They are age ≥ 45 years, BMI ≥ 50 kg/m^2, hypertension, male gender and pulmonary embolism [1, 5].

A multicenter Brazilian study showed that due to the use of IGB for 6 months, patients with obesity lost an average of 26.1 kg (3.6—77.0 kg), the average %EWL was 23.5 % (3.0—54.0 %), the average BMI decreased by 8.5 kg/m^2 (1.3—24.9 kg/m^2), the clinical picture of comorbid conditions (hypertension, diabetes, sleep apnoea, etc.) improved [13].

A study of the effect of IGB on body weight loss and comorbidity, conducted at the University of Padova (Italy) showed that the use of IGB for 164.4 ± 39.7 days (92—240 days) led to a decrease in body weight by 26.4 ± 10.2 kg (5.0—53.0 kg), the average %EWL was 26.1 ± 9.3 % (5.1—55.2 %), the average BMI decreased from 58.4 ± 6.6 kg/m^2 to 49.3 ± 6.2 kg/m^2 ($p < 0.001$), decreased surgical risk [14].

In the analysis of 30 studies involving 4,877 patients, it was shown that the use of IGB BIB led to a decrease in body weight by 4.9—28.5 kg (average — 17.8 kg), and BMI by 4.0—9.0 kg/m^2. In principle, comorbid conditions disappeared or improved in 52—100 % of these patients [15].

Thus, the presence of super-obesity is a direct indication for bariatric surgery. However, it is necessary to use effective strategies to reduce surgical risk.

Objective is to investigate the role of endoluminal interventions in the preparation of super obese patients with high risk of surgical and anaesthesia-related complications for bariatric surgery.

Materials and methods

From 2011 to 2018 97 patients with super-obesity and high risk of surgery and anaesthesia-related complications (ASA PS III—IV) underwent a course of treatment at the clinical setting of the Department of General Surgery No2 of Bohomolets National Medical University (Table 1). The study included 45 (46.4 %) men and 52 (53.6 %) women.

The treatment was carried out in 2 stages. In the main group (n = 60), the first stage of treatment included the intragastric balloon placement for a term of 6 months. The control group (n = 37) received a six-month conservative therapy focused on dietary changes, physical activity and behavioural therapy. In the second stage of treatment the patients of both groups underwent surgical procedure for the morbid obesity management [1]. The main and control groups did not have a statistically significant difference ($p > 0.05$) in gender, age and clinical variables; therefore, they were comparable. The course of the study included 6 months of the

Table 1. **Anthropometric variables in patients with super-obesity in the first stage of treatment**

Variables	Main group (n = 60)			Control group (n = 37)			p*
	Before treatment	After treatment	p	Before treatment	After treatment	p	
Body weight, kg	192.47 ± 24.85 (132—231)	163.55 ± 19.75 (115—185)	< 0.001#	190.27 ± 23.37 (128—227)	186.97 ± 19.94 (120—215)	0.051	< 0.001##
BMI, kg/m^2	68.30 ± 7.38 (53.55—77.81)	58.19 ± 7.19 (46.66—69.53)	< 0.001#	67.72 ± 9.20 (50—83.46)	66.62 ± 8.79 (48.07—83.77)	0.067	< 0.001##
Excess body weight, kg	128.41 ± 20.98 (75.6—158.6)	99.49 ± 17.31 (58.6—120.1)	< 0.001#	126.21 ± 21.39 (69.9—155.1)	122.91 ± 18.59 (63.0—149.9)	0.051	< 0.001
Actual weight loss, kg	28.92 ± 10.08 (17—52)			3.30 ± 9.94 (–15 ... +19)			< 0.001##
% EWL, %	22.46 ± 5.95 (14.30—32.79)			1.87 ± 9.25 (–19.21 ... +23.17)			< 0.001##

Data are presented as mean ± SD (min — max).
* Comparison between the main and control group after treatment.
# In one or both groups the distribution of data differs from normal, the comparison was made using the Wilcoxon signed ranks test;
in one or both groups the distribution of data differs from normal, the comparison was made using the Wilcoxon-Mann-Whitney test.

follow-up period for all patients in the first stage of treatment and 12 months — in the second stage. In this case, the time interval between the first and second stages was from 1 to 14 days.

After analysis of the anthropometric data of patients in both groups, it was noted that the mean BMI was 68.08 (95% confidence interval (CI) 66.45—69.71) kg/m^2. The mean weight of the patients was 191.63 (95% CI 186.75—196.51) kg. The fact that the vast majority of them were of working age emphasizes the medical and social significance of the problem. A co-morbidity was frequently diagnosed, in particular, hypertension was observed in 88 (90.7%) patients, coronary heart disease — in 61 (62.9%), type 2 diabetes — in 70 (72.2%) patients. The surgical and anaesthetic risk was graded as ASA PS 3.27 (95% CI 3.18—3.36). All patients with severe and life-threatening systemic diseases or systemic pathology were assigned to ASA PS III and IV.

The endoluminal therapy included the application of an intragastric balloon (IGB), namely Orbera™ Intragastric Balloon System produced by Apollo Endosurgery, Inc [6]. Prior to the IGB placement, esophagogastroduodenoscopy was performed to exclude any oesophageal, gastric or duodenal pathology. The patients received general anaesthesia with endotracheal intubation. The bariatric team included a bariatric surgeon, an anaesthesiologist and an endoscopist.

Under direct endoscopic visualization, the Placement Catheter Assembly containing the intragastric balloon was introduced perorally and then inserted down the oesophagus into the stomach. When it was confirmed that the balloon was below the lower oesophageal sphincter, the guidewire was removed. The Luer-Lock connector on the fill tube was connected to the filling system valve. Keeping the filling system valve open, a 50 cc syringe was used to fill the balloon to 700 cc. To seal the balloon valve, a syringe was connected to the fill tube and a gentle suction was produced on the placement catheter by withdrawing the plunger of the syringe. The valve was sealed with the vacuum created. The fill tube was pulled until it was out of the self-sealing valve and removed along with the sheath through the mouth. Control gastroscopy was performed to check the location of the balloon in the stomach cavity as well as visually inspect the balloon for leakage. Additionally, ultrasound monitoring was carried out to observe the position of the balloon in the stomach.

The intragastric balloon was removed 6 months after the placement. The preparation of patients for esophagogastroduodenoscopy included administration of the endotracheal anaesthesia. Esophagogastroduodenoscopy was conducted to get a clear view of the balloon shell. A puncture needle produced by Prince medical was inserted down the working channel of the gastroscope. The needle was used to puncture the balloon and push the distal end of suction tubing through the balloon shell. The needle was removed from the tubing sleeve and suction was applied to the tube until all fluid was evacuated from the balloon. After evacuation of the maximum volume of fluid, the suction tubing was removed from the balloon and out of the working channel of the gastroscope. Under endoscopic visualization, a 2-prolonged wire grasper produced by Prince medical was inserted through the working channel of the gastroscope to remove the balloon. The 2-prolonged wire grasper helped firmly grasp the deflated balloon and extract it with minimal risk of injury to the stomach wall and oesophagus. The procedure was completed with the inspection of the duodenum, stomach, and oesophagus [2, 6].

Data were analysed with the statistical package IBM SPSS Statistics Base (version 22). All results were considered statistically significant at a value of $p < 0.05$. Quantitative data are presented as mean ± standard deviation (SD), unless otherwise stated. The normality of the data distribution was checked using the chi-square test ($p > 0.05$). The comparison was performed using the Wilcoxon sign rank criterion for related samples and the Wilcoxon-Mann-Whitney criterion for unrelated samples. Quantitative assessment of the clinical effect was performed by calculating the relative risk (RR) and its 95% CI.

Results and discussion

Before the first stage of treatment, a comparative analysis of body weight and other anthropometric variables was performed in the main and control groups (see Table 1). The findings did not reveal any statistically significant difference ($p > 0.05$) between the main and control groups before treatment.

The outcomes of the first stage of treatment showed that the patients, who underwent the IGB placement, had statistically significantly ($p < 0.001$) higher mean %EWL than the patients who received conservative therapy (see Table 1).

Six months after the IGB placement there was observed a statistically significant ($p < 0.001$) decrease in the mean systolic blood pressure (SBP) and the mean diastolic blood pressure (DBP) from 170.48 (95% CI 166.90—174.07) mm Hg to 150.30 (95% CI 147.47—153.13) mm Hg and from 104.88 (95% CI 102.97—106.79) mm Hg to 87.93 (95% CI 86.42—89.45) mm Hg, respectively. Ejection fraction (EF) increased from

46.69 (95 % CI 45.36—48.02) % to 49.55 (95 % CI 48.58—50.52) % ($p < 0.001$).

The study of the external respiration function parameters revealed the prevalence of the restrictive spirometric pattern in patients with morbid obesity. Six months after the IGB placement, the patients of the main group exhibited the unidirectional dynamics of mean values of vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), maximum expiratory flow at 25 % VC (MEF25), maximum expiratory flow at 50 % VC (MEF50), maximum expiratory flow at 75 % VC (MEF75), in the direction of their growth, which was interpreted as statistically significant. Notably, our study established the growth of FVC from 60.87 (95 % CI 59.56—62.18) % to 73.25 (95 % CI 71.84—74.66) % ($p < 0.001$).

Type 2 diabetes mellitus (DM) was diagnosed in the vast majority of patients in both groups. Thus, the glycosylated haemoglobin (HbA1c) test confirmed DM in 46 (76.7 %) patients in the main group and 24 (64.9 %) patients in the control group. 13 (21.7 %) patients of the main group and 11 (29.7 %) patients of the control group had an increased risk of developing type 2 DM according to the ADA criteria (2018).

In patients of the main group, who underwent the IGB placement, the level of fasting plasma glucose and the level of glycosylated haemoglobin (HbA1c) decreased from 8.90 (95 % CI 8.43—9.36) mmol/L to 7.86 (95 % CI 7.43—8.29) mmol/L and from 7.38 (95 % CI 7.09—7.67) to 6.71 (95 % CI 6.44—6.97) respectively, in both cases $p < 0.001$. In the control group, the dynamics of these values did not reach the degree of statistical significance. It indicates the insufficient impact of conservative therapy. After the first stage of treatment that lasted 6 months, the level of fasting plasma glucose and the level of glycosylated haemoglobin in the main group were statistically significantly lower than in the control group ($p = 0.028$ and $p = 0.025$, respectively).

Before treatment, all patients of both groups were assigned to ASA PS III—IV, in accordance with the inclusion criteria of this study. An overview of the first stage of treatment in terms of surgical and anaesthetic risk in the main and control groups suggests that the patients, who underwent the IGB placement, had statistically significantly ($p < 0.001$) lower risk than the patients who received conservative therapy. In this case, the average ASA PS score in the main group decreased from 3.28 (95 % CI 3.17—3.40) to 2.15 (95 % CI 2.06—2.24; $p < 0.001$), in the control group — from 3.24 (95 % CI 3.10—3.39) to 3.14 (95 % CI 2.96—3.31; $p > 0.05$) (Table 2).

The IGB placement for a term of 6 months reduces the initially high ASA PS score. It is essential for the first stage of treatment of patients with super-obesity and their preparation for bariatric surgery [1].

By %EWL, an indicator of the effectiveness of treatment, the patients in the main and control groups were assessed as %EWL < 20 % or %EWL ≥ 20 %. It has been established that the IGB placement results in a 3 times ($p < 0.001$) reduction of the risk of failure to achieve %EWL ≥ 20 in comparison with the conservative treatment methods, RR = 0.33 (95 % CI 0.22—0.47).

The IGB placement and removal were uneventful and without any complications. Short-term mild nausea was observed in 17 (28.33 %) patients and temporary discomfort in the epigastric region was seen in 22 (36.66 %) patients.

All patients of the main group, who underwent a 6-month treatment that involved the IGB placement as the preparation for bariatric surgery, were qualified for the second stage of treatment that included surgery, the mean %EWL was 22.46 (95 % CI 20.93—24.0) %. Only 1 (2.7 %) patient in the control group met the criteria for bariatric surgery. 51 (83.6 %) patients underwent Laparoscopic Roux-en-Y Gastric Bypass (LRYGB), 9 (14.8 %) patients — Laparoscopic Adjustable Gastric Banding (LAGB), 1 (1.6 %) patient — Laparoscopic Sleeve Gastrectomy (LSG). 12 months after surgery, the mean %EWL was 55.27 (95 % CI 53.32—57.23).

The safety analysis of the surgical methods applied in the treatment of patients with morbid obesity was also conducted. Thus, no complications were observed during the intraoperative period. Among general surgical postoperative complications, purulent wound infection was detected in 2 (3.3 %) patients with super-obesity. No specific postoperative complications were noted. There was no postoperative mortality among patients.

Table 2. **Distribution of patients by level of surgical and anaesthetic risk according to ASA PS in patients with super-obesity in the first stage of treatment**

ASA PS, class	Main group (n = 60)		Control group (n = 37)	
	Before treatment	After treatment	Before treatment	After treatment
I	0	0	0	0
II	0	51 (85.0 %)	0	3 (8.11 %)
III	43 (71.67 %)	9 (15.0 %)	28 (75.68 %)	26 (70.27 %)
IV	17 (28.33 %)	0	9 (24.32 %)	8 (21.62 %)

The debatable question is whether there are enough endoluminal methods for the treatment of these patients with MO. Thus, according to a study by L. Angrisani (2006), after removal of IGB 49.4 % of patients with a baseline BMI of 54.4 ± 8.1 kg/m^2, who were scheduled for further bariatric interventions, abandoned the latter. IGB was used as an independent method of treatment. However, it is important to note that their body weight returned to baseline after 12 months [16]. One of the reasons for insufficient weight loss or re-gain is non-compliance with the patient's appointments after bariatric interventions of the prescribed diet, excess caloric intake and sedentary lifestyle.

According to the WGO Global Guideline Obesity (2011), the use of IGB can help to form a certain stereotype of eating behaviour [17]. It has been shown that the use of IGB alone in patients with a BMI ≥ 40 kg/m^2 is ineffective because after removal of the balloon, patients either completely lost weight or lost weight [3]. This may be thought to be due in particular to «balloon cheating».

Thus, endoluminal procedures, especially the establishment of IGB, play an important role in the treatment of obese patients, but their use cannot be considered as the only and radical method of bariatric intervention in obese patients, especially morbid [2].

Conclusions

The presence of surgical and anesthetic risk graded as ASA PS III—IV in patients with super-obesity and the mean BMI of 68.08 (95 % CI 66.45—69.71) kg/m^2 complicated by pathologies of the cardiovascular system, impaired external respiration and poor carbohydrate metabolism necessitates the application of two-stage treatment involving the preparation of patients for bariatric surgery in the first stage.

The intragastric balloon placement for a term of 6 months ensures efficient preparation of super obese patients for bariatric surgery as it contributes to surgical and anesthetic risk reduction from 3.28 (95 % CI 3.17—3.40) to 2.15 (95 % CI 2.06—2.24; $p < 0.001$), a decrease in BMI from 68.3 (95 % CI 66.39—70.20) to 58.19 (95 % CI 56.33—60.04) kg/m^2 ($p < 0.001$), and the improved function of the cardiovascular and respiratory systems as well as better carbohydrate metabolism.

Declaration of interests

The authors declare no conflicts of interest.

Funding. The work is a fragment of the planned research work of the Department of General Surgery No2 of Bohomolets National Medical University «Implementation of minimally invasive surgical techniques in the treatment of pathologies of the abdominal cavity, anterior abdominal wall, morbid obesity by fast-track technique» (State registration number 0118U000147).

Author contributions

O. Y. Ioffe: work concept and design, critical review, final approval of the article; M. S. Kryvopustov: data collection and analysis, statistical analysis, writing the article; O. P. Stetsenko, T. V. Tarasiuk, and Y. P. Tsiura: data collection and analysis, critical review.

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Роль ендолюмінальних втручань у підготовці пацієнтів високого ризику із суперожирінням до баріатричної операції

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Ожиріння призводить до підвищення рівня захворюваності, інвалідності та смертності, а також впливає на якість життя. З огляду на відомі ризики для здоров'я пацієнта, Міжнародна федерація хірургії ожиріння та метаболічних розладів (IFSO) приділяє особливу увагу проблемі морбідного ожиріння (індекс маси тіла ≥ 40 кг/м^2) з акцентом на суперожирінні (індекс маси тіла ≥ 50 кг/м^2).

Мета — вивчити роль ендолюмінальних втручань у підготовці пацієнтів із суперожирінням з високим ризиком хірургічних та анестезійних ускладнень до баріатричної хірургії.

Матеріали та методи. У період з 2011 до 2018 р. 97 пацієнтів із патологічним ожирінням та високим ризиком хірургічних і анестезіологічних ускладнень (ASA PS III—IV) пройшли курс лікування на клінічній базі кафедри загальної хірургії № 2 Національного медичного університету імені О. О. Богомольця. Лікування проводили в два етапи. В основній групі (n = 60) перший етап лікування передбачав внутрішньошлункову установку балона на термін 6 міс. Контрольна група (n = 37) отримувала 6-місячну консервативну терапію. Другим етапом пацієнтам обох груп виконано оперативне втручання з метою лікування морбідного ожиріння.

Результати. Результати першого етапу лікування показали, що у пацієнтів, яким проведено внутрішньошлункову установку балона, був статистично значущо ($p < 0{,}001$) вищий середній відсоток втрати надлишкової маси тіла, ніж у пацієнтів, які отримували консервативну терапію. В основній групі середній бал за ASA PS (індикатор анестезіологічного та хірургічного ризику) знизився з 3,28 (95 % довірчий інтервал (ДІ) 3,17—3,40) до 2,15 (95 % ДІ 2,06—2,24; $p < 0{,}001$), а у контрольній групі — з 3,24 (95 % ДІ 3,10—3,39) до 3,14 (95 % ДІ 2,96—3,31; $p > 0{,}05$).

Висновки. Результати дослідження свідчать, що внутрішньошлункова установка балона на термін 6 міс знижує ризики хірургічного втручання і анестезії, поліпшує функції серцево-судинної та дихальної систем, а також прискорює вуглеводний обмін, тому цей підхід можна запропонувати для підготовки пацієнтів із суперожирінням з високим ризиком хірургічних ускладнень і ускладнень, пов'язаних з анестезією, до баріатричної хірургії.

Ключові слова: морбідне ожиріння, баріатрична хірургія, цукровий діабет 2 типу.

FOR CITATION

Ioffe OY, Kryvopustov MS, Stetsenko OP, Tarasiuk TV, Tsiura YP. The role of endoluminal interventions in the preparation of high-risk patients with super-obesity for bariatric surgery. General Surgery (Ukraine). 2021:1;18-23. http://doi.org/10.30978/GS-2021-1-18.

UDC 616.411-001-036.17-089
DOI http://doi.org/10.30978/GS-2021-1-24

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Changes in the filtration function of the spleen after surgery following traumatic organ injuries

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The incidence of splenic injuries among all closed injuries of the abdominal cavity is from 15.5 to 30.0 %, and a mortality rate is between 7 % and 26 %. The tactics in the treatment of splenic injuries is determined by the degree of traumatic injury, the patient's condition during the operation, and a concomitant pathology. Studies of tissue regeneration of the operated spleen allow identifying two main options for its regeneration, associated with the nature of blood circulation in the preserved part.

OBJECTIVE — to study the regeneration and filtration function of the spleen after various types of surgery for the management of traumatic spleen injuries.

MATERIALS AND METHODS. The results of treatment of 85 patients in the period 2015—2020 were analyzed. To investigate the changes in the filtration function of the spleen, a study of the peripheral blood (general blood test) was performed to assess the shape of erythrocytes. In order to determine the size of the residual splenic parenchyma, its structure and regenerative processes were evaluated and sonographic examination was carried out.

RESULTS. The average increase in the size of the residual splenic tissue after subtotal resection of the organ with the formation of couplings of the parenchyma averages 40.2 ± 3.4 % one year after surgery, and in patients who underwent subtotal resection of the spleen with covering the cut plane with adhesive hemostatic plate 70 % — 49.14 ± 6.77 %. The study of changes in the filtration function of the spleen in patients, who underwent subtotal resection of the spleen, showed the appearance of target cells, acanthocytes and halocytes in the peripheral blood, but their number was insignificant and did not exceed normal (not more than 3 %). Any destroyed and pathologically altered erythrocytes were not visualized in patients, who underwent atypical resection of the spleen (mass deficit less than 30 %).

CONCLUSIONS. Spleen regeneration is determined both by the nature of blood supply to the residual splenic tissue and its size, and does not depend on the nature of the pathological process. Organ-preserving surgical interventions on the spleen allow maintaining the filtration function of the spleen.

KEYWORDS
spleen damage, organ-preserving surgical interventions, splenectomy, filtration function, regeneration.

ARTICLE • Received 2021-11-16 • Received in revised form 2021-11-24

The spleen is an unpaired peripheral organ of lymphoid hematopoiesis and immune defense. Currently, one of the urgent problems of surgery is control of bleeding caused by the damage to the parenchymal organs of the abdominal cavity associated with injuries resulting from home-related and traffic accidents, natural disasters and terrorist acts. These conditions, based on the data from the World Health Organization studies conducted in cooperation with the Harvard Center for Prospective Studies, are a common cause of death among people of working age. The incidence of splenic injuries among all closed injuries of the abdominal cavity is from 15,5 to 30 %, and a mortality rate is between 7 % and 26 %. [1]. Traumatic injuries occur in all age groups, but the peak incidence is observed in adolescence and in the middle age group (15—35 years) [2], which emphasizes the socio-economic importance of the problem.

The tactics in the treatment of splenic injuries is determined by the degree of traumatic injury, the patient's condition during the operation, and

a concomitant pathology. To date, the most common method of treating splenic injuries has been surgery [3]. In about 99 % of adult patients, the spleen was completely removed. However, this surgery can lead to severe complications, both in the early and long postoperative periods, resulting from impaired immunological homeostasis and is called «postsplenectomy hyposplenism», an extremely severe form of which is instantaneous sepsis [4].

In-depth experimental and clinical studies of tissue regeneration of the operated spleen, allow us to identify two main options for its regeneration, related to the nature of blood circulation in the preserved part. The first option is typical for organ-saving interventions, when the organ or its part has a preserved main blood supply. The spleen in the postoperative period has a characteristic histological structure with the presence of elements of both red and white pulp. Computed tomography (CT) examination (including after intravenous amplification) reveals normal densitometric characteristics of organ tissue. γ-Scintigraphy with labeled autologous erythrocytes, damaged by heat, shows a sufficient accumulation of radiotherapy in the pulp of the spleen (preserved filtration function) [5].

The second type of regeneration is described in humans with free heterotopic autotransplantation of the spleen [6]. The slow regeneration of the structures of the spleen pulp is typical and associated with the germination of capillaries from the surrounding tissues, developing reticular tissue filled with erythrocytes (analog of red pulp), elements of white pulp are absent or weak [7]. Densitometric analysis of CT reveals a decrease in the density of transferred and newly formed tissue with a weak accumulation of contrast after its intravenous administration [8]. The accumulation of radiotherapy in γ-scintigraphy is observed in the projection of the graft only in the remote postoperative period. The features of the autotransplanted spleen tissue in adults are the following [9].

I. The main anatomical changes

1. Reduced weight (< 20 % of normal).
2. Decrease in the number of cells in a gram of tissue.
3. Decreased blood flow (< 10 % of normal).

II. Architectural changes

1. Structures that are in the normal spleen, but changed in the graft:
- relatively reduced area of trabeculae, marginal zone, marginal sinus, PALS (periarterial lymphocyte clusters), PALS reticulum, separation of red and white pulp;
- relatively increased area of the capsule, red pulp, increased hematopoiesis.

2. Structures that are absent in the normal spleen, but are in the graft:
- fibrous tissue;
- adipocytes in the central zone;
- location of white pulp directly under the capsule;
- accumulation of lymphocytes under the capsule;
- some proteins.

III. Functional changes: reduced filtration function, clearance, malaria protection and overwhelming post-splenectomy infection.

Negative factors include inflammatory complications after autotransplantation, which in emergency and purulent surgery can reach 30 % with extraperitoneal location of fragments of the spleen [10]. Based on the described patterns, we can expect a better functional result while preserving the organ or a part of it along with the main blood supply. This is confirmed by many reports, according to which autotransplantation of the spleen is accompanied by less pronounced immunohematological changes, compared with splenectomy, but is inferior to organ-sparing operations [11]. At the same time, according to the literature, removal of 90 % of the spleen does not lead to the development of hyposplenism [12]. The presented data significantly changed the tactics in the management of the diseases of the spleen.

Thus, the spleen is an organ endowed with important functions in the body. Splenectomy causes a number of serious disorders that have certain clinical manifestations. There are methods of clinical, laboratory and instrumental assessment of the structure and functions of the spleen, as well as hyposplenic manifestations.

Objective — to study the regeneration and filtration function of the spleen after various types of surgery for the management of traumatic spleen injuries.

Materials and methods

According to the analysis of case histories, 156 patients with splenic trauma were operated at the clinic of the Department of Surgery No 2 at Bogomolets National Medical University (on the basis of the 1st and 2nd surgical departments of hospital No 4 in Kyiv) from 2015 to 2020. In order to study the condition of patients, including filtration function of the spleen, we arranged appointments with the operated patients by writing to them. Patients were invited to come to the clinic and undergo outpatient examination (laboratory and instrumental (sonographic). 85 (54.49 %) operated patients responded. The study included 61 (71.76 %) men and 24 (28.24 %) women. In terms of age distribution

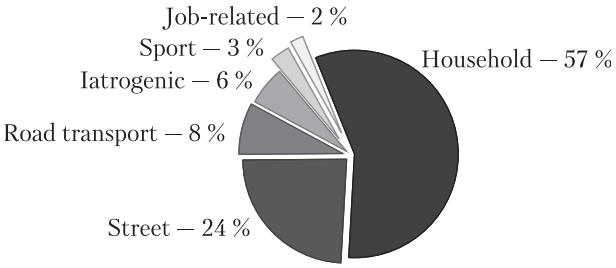

Figure 1. **Distribution of patients with traumatic injuries of the spleen by the nature of the injury**

of splenic injuries, the majority (30.18 %) were patients aged 20—29 years, while the average age of patients was 37.61 ± 11.43 (n = 106), i.e. persons of working age. The causes of injury to the spleen were: a blunt trauma — 68 (80 %) cases; a knife wound — 17 (20 %) cases. The distribution of patients by the nature of the injury is shown in Fig. 1.

Of the total number of the examined patients, 63 (74.11 %) patients had a history of isolated injuries of the spleen, 22 (25.89 %) were operated on for combined and multiple injuries.

According to the classification of splenic injuries proposed by the American Association of Surgical Trauma [13], 8 (9.41 %) patients were classified as splenic injuries, 18 (21.18 %) patients with II degree injuries, and 28 (32.94 %) patients with III degree, 23 (27.07 %) patients with IV degree and 6 (7.04 %) patients with V degree. 5 (5.88 %) patients were diagnosed with post-traumatic cyst of the spleen. Later, given the size of the residual splenic tissue, these patients were classified as patients with grade II damage to the spleen. The types of surgical interventions that were performed are presented in Table.

As can be seen from the table, a predominant number of the examined patients underwent organ-saving interventions (82.3 %). However, the analysis of their case histories revealed that the proportion of patients whose spleen was removed was 36 %

Table. **Types of surgical interventions for splenic injuries**

Method of surgical intervention	Amount (n = 85)
Standard splenectomy	15 (17.7 %)
Subtotal resection of the spleen (weight deficit is more than 70 %)	35 (41.2 %)
Atypical resection of the spleen (weight deficit is less than 30 %)	25 (29.4 %)
Minimally invasive interventions (electrocoagulation, splenoraphy, fenestration of the cyst)	10 (11.7 %)

(compared to 17.7 % in this study). Along with the traditional operations (cyst fenestration, electrocoagulation, splenoraphy, atypical resection of the spleen), patients underwent organ-sparing interventions, which were carried out using the methodology developed at the Department of Surgery N 2. These were techniques that allowed to preserve part of the parenchyma in severe traumatic injuries of the organ (III-V degrees) (the method of subtotal resection of the spleen with cutting of couplings around the arteries of the second order and the method of subtotal resection of the spleen with covering the cut plane with adhesive hemostatic plate).

To study the changes in the filtration function of the spleen (mechanical blood purification function) in the early postoperative period, the peripheral blood (general blood test) was checked to detect aging, damaged erythrocytes, pathological cells (spherocytes, sickle cells, etc.), as well as assess the shape of erythrocytes. However, upon careful study of the hemogram, we found that the shape of erythrocytes also depended on the method by which blood was taken for analysis. We compared the informativeness of the methods of studying the filtration function of the spleen during the collection of venous and capillary blood.

Results and discussion

Analyzing the nature of surgical interventions, which were performed in different time periods, we can say that the concept of choosing the method of surgical intervention in patients with splenic trauma has changed dramatically. Since 2015, the organ-preserving approach has prevailed. Even in case of severe organ damage (IV—V degree), a subtotal resection of the spleen is performed. For post-traumatic cysts of the spleen, laparoscopic surgical techniques (fenestration of cysts) are most commonly used.

Ultrasound examination of the abdominal cavity allowed visualization of the residual splenic parenchyma, assessment of its structure and characteristics of the regenerative processes after the application of organ-saving techniques. The spleen, including the structure of the left parenchyma, was studied, and a doppler investigation was ordered to evaluate blood flow and verify the detected parenchymal formation. The size of the spleen stump was determined by using an associated software package after measuring its largest size in two-dimensional orientation and delineation. The sonograms, which were performed in the early postoperative period and recorded in the patient's case history, were used as a control measurement (Fig. 2). The study of the spleen in patients, who underwent subtotal

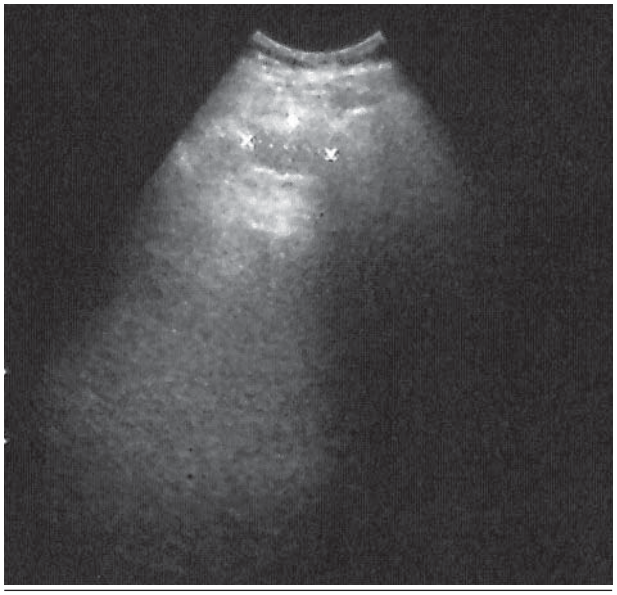

Figure 2. **Ultrasound scan of the left area of the parenchyma after subtotal resection of the spleen with the formation of couplings of the parenchyma (on day 10 of the early postoperative period)**

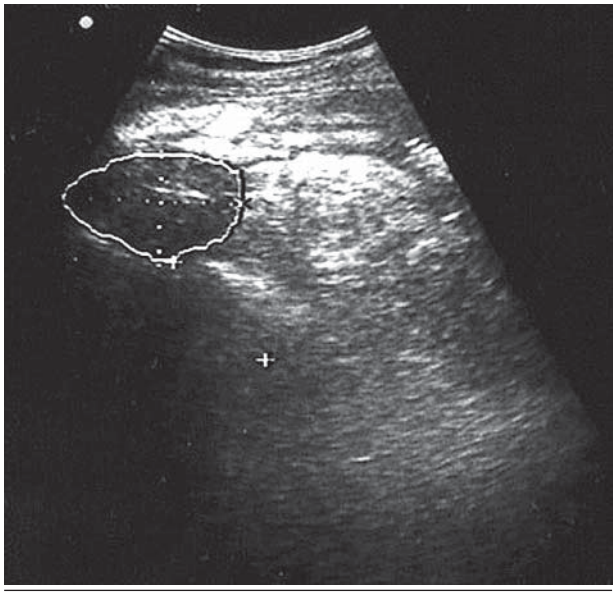

Figure 3. **Ultrasound scan of the left area of the parenchyma after subtotal resection of the spleen with the formation of couplings of the parenchyma one year after surgery**

resection of the spleen with the formation of parenchymal couplings (parenchymal deficit was more than 70 %) in the remote postoperative period, revealed a decrease in heterogeneity and an increase in the size of the residual splenic parenchyma. Analyzing the obtained data, we found out that the average increase in the size of the spleen after subtotal resection of the organ with the formation of couplings of the parenchyma one year after surgery averages 40.2 ± 3.4 % compared to baseline. Ultrasound data of the left area of the parenchyma of the spleen two months after surgery are presented in Fig. 2 and 3.

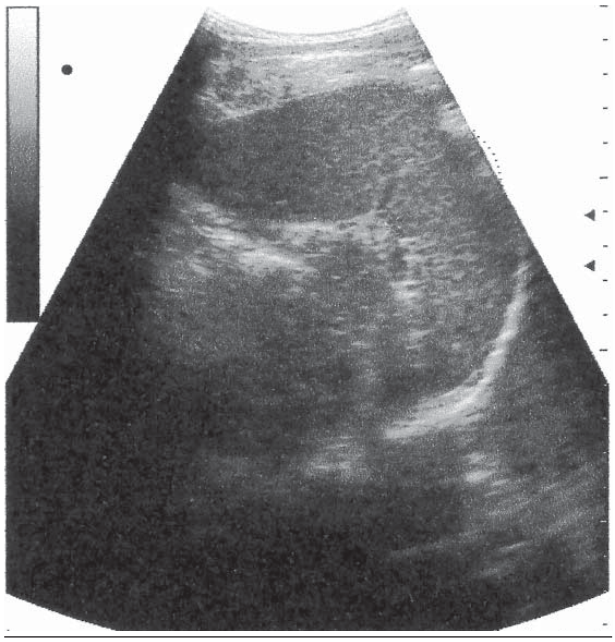

Figure 4. **Ultrasound scan of the spleen after subtotal resection of the organ with covering the plane of the cut with an adhesive hemostatic plate (4 years after surgery)**

In patients, who underwent subtotal resection of the spleen with covering the incision plane with adhesive hemostatic plate (parenchymal deficit was less than 70 %), there was a more intense increase in the size of the left parenchyma, which, in our opinion, can be associated with a larger surface area of the left parenchyma (a year after surgery, an increase in the size was 49.14 ± 6.77 % compared to baseline). In one patient, 4 years after subtotal resection of the spleen with covering the plane of the cut with an adhesive hemostatic plate, complete restoration of the structure and size of the spleen was noted (Fig. 4).

The data described above allow us to conclude that the regeneration of the spleen is determined by the nature of blood supply to the residual splenic tissue and its size, and does not depend on the nature of the pathological process.

Analyzing different ways of blood collection for the study of the filtration function of the spleen, it was found that when taking venous blood, the assessment of changes in erythrocytes can not be considered informative. This is due to the fact that according to the method, blood is taken into a test tube that contains an anticoagulant. Its components (for example, Trilon-B or citrate) affect erythrocytes, changing their shape (Fig. 5).

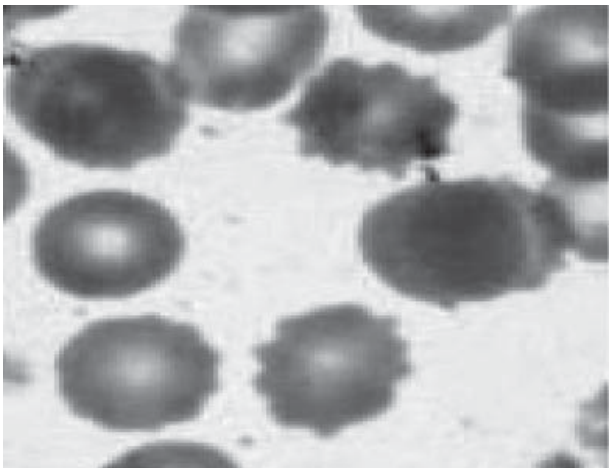

Figure 5. **Examination of red blood cells in patients after organ-sparing surgery on the spleen by venous blood sampling,** Pappenheim staining, lens × 100, microscope Olympus CX 41 (Japan): change in the shape of erythrocytes

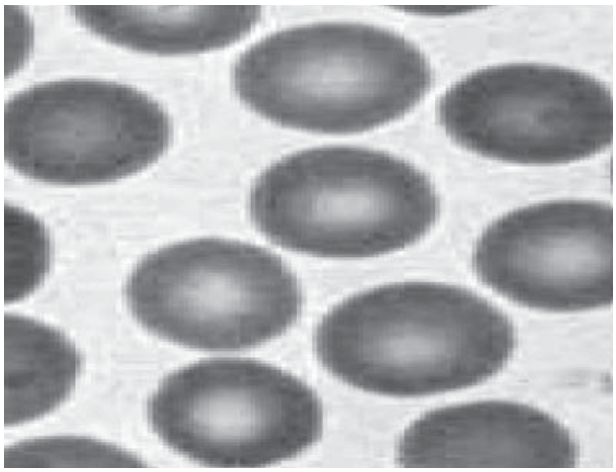

Figure 6. **Examination of red blood cells in patients after organ-sparing surgery on the spleen by capillary blood collection,** Pappenheim staining, lens × 100, microscope Olympus CX 41 (Japan): normal erythrocytes

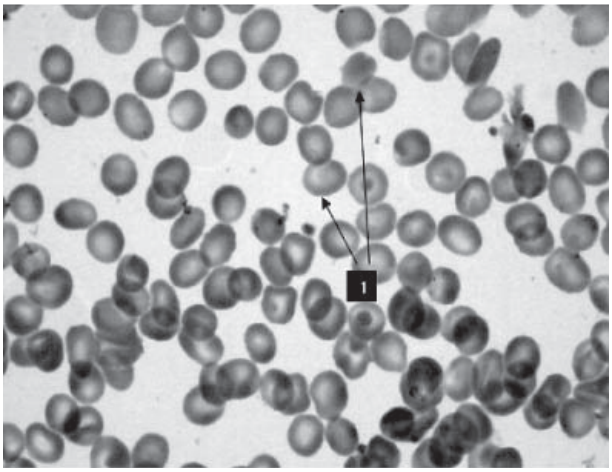

Figure 7. **Examination of red blood cells in patients after subtotal resection of the spleen — a deficit of more than 70 %,** Pappenheim staining, lens × 100: 1 — single target cells

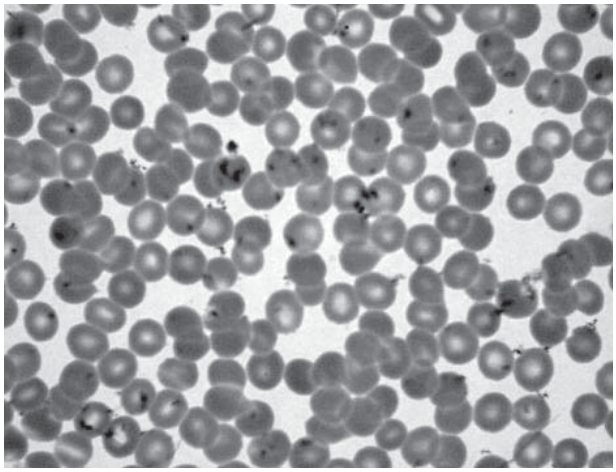

Figure 8. **Examination of red blood cells in patients after atypical resection — removal of less than 30 % of the parenchyma,** Pappenheim staining, lens × 100; pathologically altered erythrocytes were not detected

To objectively assess the changes in the hemogram in the norm and in pathological conditions, it is necessary to use a second drop of capillary blood when taking it directly from the finger on the slide (Fig. 6).

When studying changes in the filtration function of the spleen in patients who underwent subtotal resection of the spleen (mass deficit of more than 70 %), the appearance of target cells, acanthocytes and halocytes in the peripheral blood was observed, but their number was insignificant and did not exceed normal (not more than 3 %). The appearance of fragmented, damaged erythrocytes, as well as changes in the chromium of erythrocytes in the studied blood samples, was not observed (Fig. 7).

In the blood samples of patients who underwent atypical resection of the spleen (mass deficit of less than 30 %), destroyed and pathologically altered erythrocytes were not visualized or their number did not exceed normal. This fact can be explained by a larger surface area of the splenic parenchyma that is preserved during surgery and less traumatizing surgical procedure, both resulting in more efficient functioning of the left parenchyma in the postoperative period. The described data are presented in Fig. 8.

After splenectomy, a considerable impairment of the filtration function of the organ was manifested by a significant number of destroyed (fragmented) erythrocytes, pathological cells (spherocytes, sickle

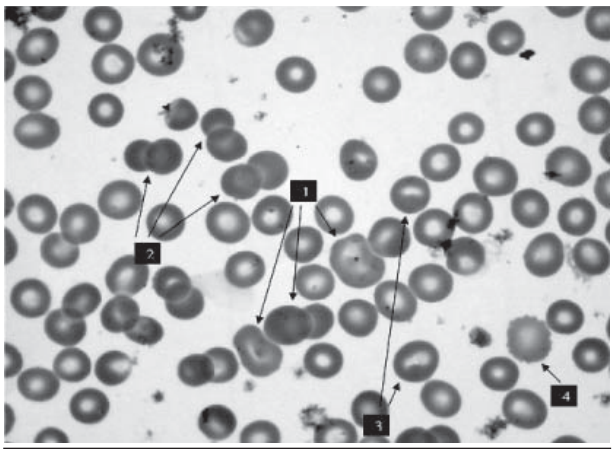

Figure 9. **Examination of red blood cells in patients after splenectomy,** Pappenheim staining, lens × 100:
1 — severe anisocytosis, with the presence of giant erythrocytes; 2 — erythrocyte hyperchromia;
3 — a significant number of stomatocytes;
4 — acanthocyte

cells, target cells, acanthocytes, etc.), erythrocytes with different hemoglobin size and content in peripheral blood (Fig. 9).

Thus, taking into account the described data, we can conclude that the presence of even a small amount of the splenic parenchyma and normal blood flow through it ensure maintenance of the filtration function of the organ, while removal of the spleen is associated with serious disorders of the organ. erythrocytes in excess of normal (more than 3 %).

Conclusions

Regeneration of the spleen is determined by the nature of blood supply to the residual splenic tissue and its size, and does not depend on the nature of the pathological process.

Organ-preserving surgical interventions, including subtotal resection of the organ, allow the spleen to perform its filtration function (destroyed and pathologically altered erythrocytes were not visualized or their number did not exceed normal).

Splenectomy leads to serious and persistent changes in the patient's hemogram (appearance of a significant number of destroyed (fragmented) erythrocytes, pathological cells (spherocytes, sickle cells, target cells, acanthocytes, etc. in the peripheral blood).

To objectively assess the hemogram, capillary blood sampling from a finger (the second drop is taken directly on a glass slide) must be performed.

The use of venous blood for research is uninformative due to the damaging effect of the preservative on erythrocytes.

Author contributions

I. V. Kolosovych: conception or design of the work, drafting the aricle, critical revision of the article; I. V. Hanol: data collection, data analysis and interpretation, drafting the article.

Declaration of interests

The Authors declare no conflicts of interest.

Funding. The work was performed in accordance with the plan of the research work of the Department of Surgery N 2 of Bogomolets National Medical University: «Development and implementation of methods for diagnosis and treatment of surgical pathology of the abdominal cavity and blood circulation». The authors did not receive any additional financial support.

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Зміни фільтраційної функції селезінки після оперативних втручань з приводу травматичних ушкоджень органа

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Частота травматичних ушкоджень селезінки серед усіх закритих травм органів черевної порожнини становить від 15,5 до 30,0 %, летальність складає 7—26 %. Тактика і спосіб лікування визначаються ступенем травматичного ушкодження, станом хворого під час операції та наявністю супутньої патології. Дослідження регенерації тканин прооперованої селезінки дають змогу виділити два основних варіанти її регенерації, пов'язані з характером кровообігу в збереженій частині.

Мета — вивчити регенераційну та фільтраційну функції селезінки після різних видів операцій з приводу її пошкодження.

Матеріали та методи. Проаналізовано результати лікування 85 пацієнтів за період 2015—2020 рр. Для вивчення змін фільтраційної функції селезінки проводили дослідження периферичної крові хворих (загальний аналіз крові) з оцінкою форми еритроцитів. Для візуалізації залишеної частини паренхіми селезінки, оцінки її структури та особливостей регенеративних процесів використовували сонографічне дослідження.

Результати. Середній приріст площі селезінки при застосуванні способу субтотальної резекції органа з формуванням муфт паренхіми через рік становив у середньому (40,2 ± 3,4) %, а у пацієнтів, яким було застосовано спосіб субтотальної резекції селезінки з укриванням площини зрізу клейовою гемостатичною пластиною (дефіцит паренхіми < 70 %) — (49,14 ± 6,77) %. При вивченні змін фільтраційної функції селезінки у хворих, яким була виконана субтотальна резекція селезінки, виявлено появу мішеноподібних клітин, акантоцитів і галоцитів у периферичній крові, однак їх кількість була незначною та не перевищувала показників норми (не більше 3 %). У пацієнтів, яким була виконана атипова резекція селезінки (дефіцит маси < 30 %), зруйновані та патологічно змінені еритроцити не візуалізувались.

Висновки. Регенерація селезінки визначається як характером кровопостачання тканини, що залишилася, так і її кількістю, та не залежить від характеру патологічного процесу. Органощадні хірургічні втручання на селезінці дають їй змогу виконувати фільтраційну функцію.

Ключові слова: ушкодження селезінки, органощадні хірургічні втручання, спленектомія, фільтраційна функція, регенерація.

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FOR CITATION

Kolosovych IV, Hanol IV. Changes in the filtration function of the spleen after surgery following traumatic organ injuries. General Surgery (Ukraine). 2021:1;24-30. http://doi.org/10.30978/GS-2021-1-24.

UDC 616.34-007.43-031:611.957-089.844-089.12
DOI http://doi.org/10.30978/GS-2021-1-31

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Totally extraperitoneal inguinal hernia repair versus Lichtenstein repair: a one-year follow-up study

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The inguinal hernia has an incidence of 27—43 % in males. Surgical repair is the most accepted treatment to prevent the development of complications. Laparoscopic inguinal hernia repair has become popular worldwide and includes the use of a laparoscopic technique for mesh placement behind the defect.

Objective — to assess whether totally extraperitoneal (TEP) inguinal hernia repair shows benefits over Lichtenstein repair in intraoperative and one-year follow-up postoperative outcomes for male patients with primary unilateral inguinal hernia.

Materials and methods. 53 males were randomly allocated to two groups. Group 1 included 27 patients who underwent totally extraperitoneal hernia repair using self-gripping lightweight mesh, and group 2 included 26 patients who were treated surgically with Lichtenstein repair using lightweight mesh.

Results. Both groups were comparable in mean age, type of hernia, body mass index and patient's distribution according to the European hernia society classification. TEP repair takes on average a little less time as compared to Lichtenstein repair, and this difference is not statistically significant. The mean of visual analogue scale for pain scoring in the first 24 hours after surgery as well as in the next 24 hours is statistically significantly smaller in group 1 compared to group 2. The mean time taken to return to work was 2.15 times longer in group 2 than in group 1, and the difference was statistically significant.

Conclusions. Totally extraperitoneal hernia repair shows potential benefits over Lichtenstein repair for primary unilateral inguinal hernias as it causes less pain in the postoperative period and ensures early return to work.

Keywords
totally extraperitoneal hernia repair, Lichtenstein repair, inguinal hernia, surgery.

ARTICLE • Received 2021-10-18 • Received in revised form 2021-11-01

The inguinal hernia has an incidence of 27—43 % in males. Surgical repair is the most accepted treatment to prevent the development of complications [6, 12, 13]. Mesh repair is generally preferred in inguinal hernia surgery. Open non-tension mesh hernioplasty has been the «gold standard» in inguinal hernia surgery for a long time [1]. At first, the laparoscopic inguinal hernia repair (LIHR) was introduced by R. Ger et al. in 1990 [5]. LIHR has become popular worldwide because laparoscopic placement of mesh behind the defect where, according to Laplace's Law, the same forces that cause hernia are used to reinforce the repair [4]. The totally extraperitoneal method (TEP) established by J. L. Dulucq in Europe allows access to the pre-peritoneal space and avoids the need for a peritoneal incision [3].

Objective — to assess whether totally extraperitoneal inguinal hernia repair shows benefits over Lichtenstein repair in intraoperative and one-year follow up postoperative outcomes for male patients with primary unilateral inguinal hernia.

Materials and methods

53 males with primary unilateral inguinal hernia were enrolled in the study and operated in the clinic «Medikom» from 2016 to 2019 years. Patients over 18 years of age with primary unilateral

evident uncomplicated inguinal hernia who fit for both laparoscopic and open approach were included in the study. All of them were randomly allocated to two groups: group 1 included 27 patients who underwent totally extraperitoneal inguinal hernia repair by our method (patent of Ukraine No 102998) using electric bipolar welding hemostasis and self-gripping lightweight mesh with polypropylene fibers and polylactic acid micro hooks, and group 2 included 26 patients who were treated surgically with Lichtenstein repair [10] using electric bipolar welding hemostasis and lightweight mesh. Preoperative evaluation was based on proper analysis of the medical history, full clinical examination, laboratory investigations and ultrasound of the abdominal cavity, pelvis and inguinal area. Early postoperative therapy included pain relievers, correction of cardiovascular and respiratory disorders, antibacterial and anticoagulation therapy. Table shows patient demographics and patient distribution in both groups according to the European hernia society (EHS) inguinal hernia classification [11].

The following parameters were evaluated: operating time, pain severity within the first 24 hours and within the next 24 hours after surgery (using 10-balls VAS score), postoperative complications over a 12-month follow-up period, mean time taken to return to work.

The statistical software package was used in this study. The independent 't' test was used to compare age, operating time, severity of postoperative pain, mean time taken to return to work. Quantitative data are presented as mean and average deviation from the mean (M ± m). $p < 0.05$ was considered statistically significant. Patient distribution based on EHS-classification and on direct/indirect inguinal hernia type were were analysed by Chi-square test (χ^2). $p < 0.05$ was considered statistically significant.

Table. **Patient demographics and patient distribution in both groups according to the European hernia society inguinal hernia classification**

Variable	Group 1	Group 2
Age, years	39.7 ± 2.08 (19—60)	38.62 ± 2.33 (18—61)
Inguinal hernia type direct/indirect	5/22	4/22
Body mass index, kg/m^2	24.15 ± 0.35	23.96 ± 0.38
European hernia society inguinal hernia classification		
PM1	1	1
PM2	3	2
PM3	1	1
PL1	4	5
PL2	12	10
PL3	6	7

All $p > 0.05$.
Quantitative data are presented as mean and average deviation (M ± m).
The data range is given in brackets.

Results and discussion

Table shows that the difference in mean age, type of hernia, body mass index and patient distribution according to the EHS classification was not statistically significant between the two groups. Therefore, both groups were comparable.

Indirect hernia appeared to be the most common type of hernia in both groups.

The operating time in minutes was 36.78 ± 0.61 in group 1 and 37.08 ± 0.82 in group 2 ($p > 0.05$). The difference is not statistically significant. It means that the TEP repair takes on average a little less time as compared to Lichtenstein repair.

In group 2 both inguinal nerves were recognized in 14 (53.85 %) patients, the ilioinguinal nerve in 4 (15.38 %) patients, the iliohypogastric nerve in 3 (11.54 %) patients, and no nerves in 5 (19.23 %) patients.

The pain score during the first 24 hours after surgery was 2.41 ± 0.11 balls in group 1 comparing to 3.04 ± 0.17 in group 2 ($p < 0.05$). It suggests that the difference in pain score was significant, so we can conclude that within the first 24 hours patients in group 1 had a less pain score compared to group 2.

The pain score within the next 24 hours was 1.3 ± 0.09 (M ± m) balls in group 1 versus 1.88 ± 0.09 in group 2 ($p < 0.05$). The difference is statistically significant. Thus, within the first 24 hours and within the next 24 hours, patients in the laparoscopic group experienced less pain than patients in the open surgery group.

In group 1, the postoperative complications were noted in 1 (3.7 %) patient who developed port site seroma. The seroma was punctured under ultrasound supervision.

In group 2, the postoperative complications occurred in 2 (7.69 %) patients. One of them developed surgical wound seroma, another one developed surgical wound hematoma. All these patients underwent puncture under ultrasound supervision, and the hematoma was coagulated.

The mean time taken to return to work was 7.96 ± 0.15 (M ± m) days in group 1 and 17.08 ± 0.17 (M ± m) days in group 2 ($p < 0.05$).

No wound infection, chronic pain, or recurrence was found in both groups over a 12-month follow-up period.

Surgical equipment and surgical techniques are constantly evolving, so the surgeons can choose from the most popular ones. To quote J. Bruce of Edinburgh: «The final word on hernia will probably never be written» [9]. The introduction of tension-free repair using prosthetic mesh represented a new era in inguinal hernia repair [14]. Nonabsorbable mesh types such as polypropylene, polytetrafluorethylene, and polyester were initially used for hernia repair. Among these, heavy polypropylene mesh was most commonly used because it had many benefits such as being flexible, strong, easily cut, readily integrated by surrounding tissues, and resistant to the infection. However, postoperative pain and foreign body sensation constantly bothered patients, and thus lightweight and ultralightweight meshes were developed. However, although the use of the lightweight mesh resulted in much less postoperative pain and reduced foreign body sensation compared with the use of the heavyweight nonabsorbable mesh, decreased intraoperative control and increased recurrence rates were more common. To maximize both intraoperative control and postoperative comfort as well as minimize the recurrence rates, partially absorbable prostheses have been recently developed and are made up of nonabsorbable materials, such as polypropylene as a standard, and absorbable materials, such as polyglactin that allows leaving less foreign material in the recipient's body without compromising the mechanical resistance [15].

Preperitoneal mesh reinforces the internal inguinal ring, the Hesselbach's triangle and annulus femoralis, where the inguinal hernia sac develops. Therefore, preperitoneal repair is indicated for the treatment of indirect, direct and femoral hernias. The mesh was used in group 1. It is made up of monofilament polyester and a resorbable polylactic acid gripping system which perfects true tension-free repair. The microhooks cover the entire upper side of the material and allow anchoring the mesh to the tissue. Therefore, a smaller suture is required, and there is less chance of nerve entrapment that can be a reason for postoperative pain. Thus, the use of such self-fixing mesh in laparoscopic surgery is safe and feasible and may reduce postoperative pain. Our study confirms the hypothesis that the fixation of the mesh with sutures in group 2 is a time-consuming procedure and accounts for the majority of the operating time. Consequently, open mesh repair is much more appropriate for all varieties of inguinal hernias such as sliding, irreducible, strangulated hernia as well as for patients with co-morbidity [2].

Seromas are known to be the most common postoperative complication after TEP inguinal hernia repair [15], and they also occurred most often in this study.

The mean of VAS for pain scoring within the first 24 hours after surgery as well as within the next 24 hours gives evidence of less severe acute pain in the laparoscopic repair group as compared to Lictenstein repair group and this difference is statistically significant. TEP repair produced less surgical trauma than open Lichtenstein hernia repair method. This result is similar to the results obtained in similar comparative studies done in the past [7, 8].

The mean time taken to return to work was 2.15 times longer in group 2 than in group 1. It also confirms the fact that TEP repair produced less surgical trauma than open Lictenstein hernia repair method.

There were no life-threatening complications, no recurrence of hernia over a 12-month median follow-up period in both groups. However, additional studies are necessary for further investigation of the previously observed recurrences.

The laparoscopic approach provides magnification of the surgical field for inspection of the entire myopectineal orifice well, allowing surgeons to repair any unexpected hernias simultaneously. Consequently, the recurrence rate can be reduced [3]. Our study noted the following benefits of laparoscopic surgery: less pain in the postoperative period, faster recovery and appropriate safety.

In this study, no mortalities were documented. In the literature, the mortality rate after an elective hernia repair doesn't exceed 0.2 % and is related to the existing comorbidities [13].

Conclusions

Totally extraperitoneal hernia repair shows potential benefits over Lichtenstein repair for primary unilateral inguinal hernias as it ensures less pain in the postoperative period and early return to work. Continuous innovations and improved technologies will ultimately determine whether totally extraperitoneal hernia repair will become a generally accepted method in surgery.

Acknowledgements

The authors gratefully acknowledge the support of the Bogomolets National Medical University administration and the Clinic «Medikom» administration and its staff.

Declaration of interests

Authors declare that they have no conflicts of interest.

Funding. No grants or support were used in this study.

Ethics approval and written informed consents statements

All procedures, performed in the study and involving human participants, were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from all individual participants included in the study.

Author contributions

H. O. Havrylov: the implementation of the research;
O. V. Shulyarenko: to the design of the research, the analysis of its results and manuscript writing.

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Порівняння тотальної екстраперитонеальної пластики пахової грижі та пластики за Ліхтенштейном: 1 рік спостереження

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Пахова грижа виникає у чоловіків у 27—43 % випадків. Хірургічне втручання — найбільш прийнятний метод лікування, що дає змогу уникнути розвитку ускладнень. Лапароскопічна пластика пахової грижі набула популярності у світі завдяки лапароскопічному встановленню сітки за дефектом.

Мета — оцінити переваги тотальної екстраперитонеальної пластики пахових гриж порівняно з операцією Ліхтенштейна в інтраопераційний період і протягом 1 року після операції у пацієнтів чоловічої статі з первинною однобічною паховою грижею.

Матеріали та методи. Випадковим чином 53 пацієнти розділили на дві групи залежно від способу лікування: 1-ша (n = 27) — тотальна екстраперитонеальна пластика з використанням полегшеної сітки, яка самофіксується, 2-га (n = 26) — операція Ліхтенштейна з використанням полегшеної сітки.

Результати. Обидві групи були однорідні за середнім віком, типом грижі, індексом маси тіла та розподілом пацієнтів за Європейською класифікацією герніологів. Тривалість виконання тотальної екстраперитонеальної пластики пахових гриж в середньому була статистично незначущо дещо меншою порівняно з операцією Ліхтенштейна. Середнє значення за візуальною аналоговою шкалою для оцінки болю протягом перших 24 год після операції, а також протягом наступних 24 год було статистично значущо менше в 1-й групі. Середня тривалість відновлення працездатності в 2-й групі була в 2,15 разу статистично значущо більшою, ніж у 1-й.

Висновки. Потенційні переваги тотальної екстраперитонеальної пластики порівняно з операцією Ліхтенштейна в хірургії первинних однобічних пахових гриж полягають у меншій інтенсивності післяопераційного болю і швидшому відновленні працездатності.

Ключові слова: тотальна екстраперитонеальна пластика грижі, операція Ліхтенштейна, пахова грижа, хірургія.

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FOR CITATION

Havrylov HO, Shulyarenko OV. Totally extraperitoneal inguinal hernia repair versus Lichtenstein repair: a one-year follow-up study. General Surgery (Ukraine). 2021:1;31-35. http://doi.org/10.30978/GS-2021-1-31.

UDC 616.441-008.61-097.3-089
DOI http://doi.org/10.30978/GS-2021-1-36

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Results obtained after the surgical treatment of Graves' disease depending on the levels of anti-thyroid antibodies

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Graves' disease (GD) is a hereditary autoimmune disease which is characterized by persistent abnormal hypersecretion of thyroid hormones and thyrotoxicosis syndrome development. GD affects from 0.5 % to 2.0 % of population in different regions. 46 % of these patients develop ophthalmopathy. GD is a common cause of disabilities in patients under 60 years of age. In recent years, the incidence of GD in Ukraine has increased by 9.9 % — from 106.2 to 117.9 per 100,000 individuals. This can be connected with the improved diagnostic possibilities and active disease detection as well as with the increased number of autoimmune thyroid disorders. The recent studies focus on prevention of specific complications and recurrences of GD after surgery.

Objective — to compare the levels of antibodies to the thyroid-stimulating hormone receptors (TSHR-Ab) during different postoperative periods as well as the incidence of early and late complications depending on the surgical technique used for the treatment of GD.

Materials and methods. The results of surgical treatment of 130 patients, with GD were compared. 29 male patients and 101 female patients aged from 19 to 76 (average — 44.1 ± 3.2 years), receiving their treatment for GD in Kyiv Center of Endocrine Surgery during 2010—2018, were randomly selected and divided into two groups. At the time of operation the duration of disease was from 1 to 30 years (average — 4.6 ± 1.2 years). Group 1 included 65 patients that underwent total thyreoidectomy (TT) and group 2 included 65 patients that underwent subtotal thyreoidectomy (ST). The following parameters were compared: surgery duration, the incidence of early postoperative complications, including bleedings and damage to the recurrent laryngeal nerves, and late outcomes of surgical treatment (persistent hypoparathyreoidism disorder and disorder recurrences) depending on the method of surgery (ST or TT). Furthermore, the patterns of the TSHR-Ab level reduction were studied for different postoperative periods.

Results. The comparison of surgical outcomes following TT and ST didn't reveal any statistically significant differences in such evaluation criteria as the average surgery duration, the average volume of intraoperative blood loss and the average duration of the postoperative inpatient treatment. The comparative assessment of the thyroid stump volume and the average amount of drained discharge showed statistically significant differences for TT. It allows considering TT as a surgery which causes less complications than ST. The studied parameters of early postoperative complications had no significant differences for ST and TT. The long-term (5 years) postoperative level of TSHR-Ab was statistically significantly lower in patients after TT and made up 1.15 ± 0.13 IU/L (thus corresponding to the normal level).

Conclusions. Total thyroidectomy is an optimal surgical technique and is more appropriate compared with subtotal thyroid gland resection. It should be noted that TT provides lower risk of complications due to significantly lower level of TSHR-Ab in late postoperative period.

Keywords
antibodies to the thyroid-stimulating hormone receptors, Graves' disease, subtotal thyreoidectomy, thyroidectomy.

ARTICLE • Received 2021-10-18 • Received in revised form 2021-10-22

The Graves' disease (GD) is a hereditary autoimmune disease, which is characterized by the persistent pathological hypersecretion of thyroid hormones with the thyrotoxicosis syndrome development. It develops due to the thyroid-stimulating globulins which begin to compete with thyreotrophin for its receptors and stimulate the production of thyroid hormones.

Other factors (inheritance, infectious and psychogenic effects) serve as drivers promoting autoimmune disorders. Infectious diseases (influenza, angina, chronic tonsillitis, scarlatina, pertussis, rheumatism, and encephalitis) precede, in 17—20 % of cases, the development of the clinical picture typical for GD. Nowadays, GD is considered a classical autoimmune disease which induces synthesis of the thyro-stimulating hormone (TSH) antibodies and their binding to the a-subunit of the TSH receptor on a thyrocyte membrane causes the activation of adenylate cyclase, increased levels of the intracellular cAMP (cyclic adenosine monophosphate) resulting in phosphorylation of protein kinase A and activation of transcription factors [7, 11, 17, 21]. These processes contribute to the increased iodine capture, synthesis of thyroid peroxidase and thyroglobulin, and, finally, to hyperthyroidism.

GD affects from 0.5 % to 2.0 % of population in different regions. 46 % of these patients develop ophthalmopathy [5, 25]. GD is a common cause of disabilities in patients under 60 years of age. In recent years, the incidence of GD in Ukraine has increased by 9.9 % — from 106.2 to 117.9 per 100,000 individuals. This can be connected with the improved diagnostic possibilities and active disease detection as well as with the increased number of autoimmune thyroid disorders.

Despite significant achievements in studying of GD pathogenesis, there are still many disputable issues on diagnostics and treatment strategies that need further research. Thus, the data on the levels of antibodies to the thyroid-stimulating hormone (TSHR-Ab) receptors in patients with GD during different stages of the disease and throughout early and late postoperative periods are not structured.

The treatment of GD mainly includes conservative, radioiodine and surgical therapy. However, surgery is the most frequent and preferable option since it ensures fast removal of thyrotoxicosis manifestations. The recent studies focus on prevention of specific complications and recurrences of GD after surgery.

It is believed that the amount of the remaining thyroid tissue is one of the most important factors that can be controlled by a surgeon. However, surgical operation cannot always recover the euthyroid state of a patient. Hypothyreosis or thyrotoxicosis recurrence can appear during different postoperative periods. Surgery indications and outcomes of surgical treatment are still being discussed.

Aims: The study aimed to compare the levels of antibodies to the thyroid-stimulating hormone (TSHR-Ab) receptors during different postoperative periods as well as the incidence of early and late complications depending on the surgical technique used for the treatment of GD.

Materials and methods

130 patients (29 men and 101 women aged between 19 and 76 (mean age 44.1 ± 3.2 years)), receiving their treatment for GD in Kyiv Center of Endocrine Surgery, were randomly selected and divided into two groups: group 1 included 65 patients that underwent total thyreoidectomy (TT) and group 2 included 65 patients that underwent subtotal thyreoidectomy (ST).

The following parameters were compared: surgery duration, the incidence of early postoperative complications, including bleedings and damage to the recurrent laryngeal nerves, and late outcomes of surgical treatment (persistent hypoparathyroid disorder, hypothyroidism (hypoPTH), and thyrotoxicosis recurrences) depending on the method of surgery (ST or TT). Furthermore, the patterns of the TSHR-Ab level reduction were studied for different postoperative periods.

TSHR-Ab were studied in a commercial laboratory, using a Siemens Architect 2000 analyzer for the chemiluminescent analysis. Reference values for TSHR-Ab were > 0.55 IU/ml for positive results and < 0.55 IU/mL for negative results. The parathormone level was determined immunochemically, using a Cobas 6000 analyzer for the electrochemiluminescence detection; reference values for a positive result were 15—65 pg/mL.

The obtained results were statistically processed by means of IBM SPSS Statistics Base (version 22), using various statistical methods. Student's t-test was used for the determination of the probability of average value difference. Data are provided as M ± m. The difference was considered to be statistically significant in $p < 0.05$. The inter-series correlation analysis of parameters was calculated using the χ^2 criterion (Pearson's criterion).

Results and discussion

According to the sex and age distribution, there were no statistically significant differences in groups (Table 1). The disease duration as of the moment of the surgery was from 1 to 30 years, on average 4.6 ± 1.2 years. These patients had coexisting

Table 1. **Patient demographics, patient distribution depending on the size of thyroid nodules in groups**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Male	8	5
Female	57	60
Age, years	45.3 ± 2.24	41.7 ± 2.08
Disease duration before operation, years	2.85 ± 0.22	3.1 ± 0.31
Volume of the thyroid gland, cm^3	38.53 ± 0.62	37.01 ± 0.75

All $p > 0.05$.

Table 2. **Comparative analysis of surgery parameters depending on a surgical technique**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Average surgery duration, min	110.83 ± 6.4	108.79 ± 2.39
Average volume of intraoperative blood loss, mL	84.8 ± 1.39	85.4 ± 1.46
Thyroid stump volume, cm^3	0	2.2 ± 0.06*
Average volume of drained discharge, mL	46.6 ± 0.93	65.86 ± 1.33*
Average hyperthermia duration, h	20.12 ± 0.68	20.62 ± 0.67
Average duration of postoperative inpatient treatment, days	6.77 ± 0.06	6.59 ± 0.07

* The difference between the groups is statistically significant ($p < 0.05$).

Table 3. **Comparative analysis of the incidence of early postoperative complications depending on a surgical technique**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Postoperative bleeding	2 (3.1 %)	3 (4.6 %)
Transient hipoparathyreoidism	5 (7.7 %)	6 (9.2 %)
Vocal fold paresis	5 (7.7 %)	6 (9.2 %)

All $p > 0.05$.

surgery indications, including multinodular goiter in 79 (60.8 %) patients, recurrent disease — in 80 (61.5 %) patients, cardiovascular complications — in 38 (29.2 %) patients, among which the heart valvular insufficiency with heart insufficiency (degree III) was observed in 25 (19.2 %) patients, atrial fibrillation — in 10 (7.69 %) patients; thyrotoxic ophthalmopathy was diagnosed in 38 (29.2 %) patients, presence of thyroid lesions — in 33 (25.38 %) patients, and a drug allergy — in 3 (2.3 %) patients.

The analysis of the outcomes of surgical treatment is given in Table 2.

The comparison of surgical outcomes following TT and ST didn't reveal any statistically significant differences in such evaluation criteria as the average surgery duration, the average volume of intraoperative blood loss and the average duration of the postoperative inpatient treatment.

The comparative assessment of the thyroid stump volume and the average amount of drained discharge showed statistically significant differences for TT. Thus, both surgeries have the same risk of causing complications under equal initial conditions.

Early postoperative complications are given in Table 3. There were no statistically significant differences in postoperative states of patients after ST and TT (see Table 2).

The analysis of each clinical case revealed that the early postoperative period was complicated with subcutaneous vessel bleeding in 1 patient, bleeding from the right superior artery in 2 patients, bleeding from the right vascular pedicle in 1 patient, and bleeding from the thyroid stump in 1 patient.

The symptoms of transient hypoparathyreoidism were observed on the 3th-5th day in 6 (9.25 %) patients after TT and in 5 (7.7 %) patients after ST.

It is commonly known that in most cases the vocal fold mobility is impaired due to the damage to the recurrent laryngeal nerves during surgeries [4, 6]. The recurrent laryngeal nerves can be damaged due to the deformation and anatomical mapping relationships caused by significant thyroid enlargement, anatomical proximity of the recurrent laryngeal nerve to the inferior thyroid artery, excessive use of electric coagulation, postoperative edemas, hematoma or nerve involvement into a cicatrization [20, 22].

Based on the course and duration, injuries of the recurrent laryngeal nerves are divided into two categories: transient disturbances lasting up to 6 months, and persistent disturbances which last over 6 months [10, 25].

Usually, during the early postoperative period, the available instrumental methods do not allow objective differentiation of pareses and paralyses of

Table 4. **Comperative analysis of late postoperative complicantions in pacients with GD**

Parameter	Group 1 (n = 65)	Group 2 (n = 65)
Vocal fold paresis	1 (1.5 %)	2 (3.1 %)
Persistent hipoparathyreoidism	1 (1.5 %)	3 (4.6 %)
Thyrotoxicosis recurrence	0	2 (3.1 %)

All $p > 0.05$.

Table 5. **TSHR-Ab levels (IU/mL) observed in GD patients during different postoperative periods after ST and TT**

Period	Group 1 (n = 65)	Group 2 (n = 65)
6 months	13.93 ± 3.7	19.89 ± 4.2
12 months	8.55 ± 3.08	11.61 ± 3.97
5 years	1.15 ± 0.13	5.48 ± 0.42*

* The difference between the groups is statistically significant ($p < 0.05$).

the recurrent laryngeal nerves, whereas the impaired mobility of vocal folds can be diagnosed [4, 15]. During this early postoperative period, the unilateral damage of a recurrent laryngeal nerve can cause reflex spasms of a contralateral vocal fold, thus simulating the complete laryngeal paresis [12, 16].

The analysis of each clinical case of damaged recurrent laryngeal nerves revealed hoarseness, aphonia, moderate or severe breathing disorders, and coughing fits in 16 (12.14 %) patients on the 1st postoperative day.

During the mirror laryngoscopy, paresis of a right vocal fold was detected in 3 (2.3 %) patients, paresis of a left vocal fold — in 4 (3.0 %) patients, and bilateral paresis — in 4 (3.0 %) patients, paresis of a left vocal fold, and paresis of a right vocal fold — in 2 (1.54 %) patients, paresis of a right vocal fold and paresis of a left vocal cord — in 1 (0.76 %) patient, and bilateral paresis, of vocal folds — in 2 (1.54 %) patients. The comparison of the occurrence of this complication did not show any statistically significant difference for both groups.

Thus, summarizing the results obtained during the study of early postoperative complications, we can conclude that no probable differences related to the occurrence of such complications as bleeding, hyperparathyroidism, and paresis of the recurrent laryngeal nerves were observed for both of the studied surgical methods of treatment of GD (ST and TT) (χ^2-test according to the criterion).

Late postoperative complications include vocal fold paresis, persistent hyperparathyroidism and recurrences of thyrotoxicosis. The development of these late postoperative complications was analyzed based on the clinical and hormonal examination of patients within periods from 6 to 12 months (for vocal fold paresis, and persistent hyperparathyroidism) and five years (for thyrotoxicosis recurrences) after the surgery.

The analysis of late postoperative complications in patients with GD is given in Table 4.

No statistically significant difference was detected for the occurrence of vocal fold paresis, persistent hyperparathyroidism and thyrotoxicosis recurrence in the study groups. After surgeries (ST and TT), the postoperative hypothyroidism was diagnosed in 124 (95.4 %) patients; after ST surgeries, the euthyroid state was observed in 6 (4.6 %) patients, and two of them had delayed thyrotoxicosis recurrences: after 16 months and within 24 months after surgery. The radioiodine treatment was administered in case of thyrotoxicosis recurrences (I^{131}).

All patients with postoperative hypothyroidism (95.4 %) were prescribed thyroid hormones (Euthyrox, L-thyroxin) as the substitution therapy. Daily doses of hormonal drugs in the group of patients after ST was 125.5 ± 12 μg, and in the group of patients after TT — 131.75 ± 14 μg. Thus, no probable difference in the thyroid hormone doses was observed for patients of both groups ($p > 0.05$).

According to the aims of the study, a comparative analysis of TSHR-Ab levels during different postoperative periods was carried out. The patterns of the reduction of TSHR-Ab levels in ST and TT patients one year after surgery and in the late (5 years) period after it were studied. Table 5 provides levels of TSHR-Ab during different post-ST and post-TT periods.

The long-term observation (5 years) showed that the TSHR-Ab level reduced by 76.2 % (compared with the initial value) in the group after ST, and by 91.7 % — in the group after TT. The difference is statically significant ($p < 0.05$). The post-TT level of TSHR-Ab was 1.15 ± 0.13 IU/L, thus corresponding to the normal level. However, the same improvement was not observed in ST patients. After ST, the TSHR-Ab level for the same period was statistically significantly higher than reference levels.

The analysis of the patterns of the TSHR-Ab levels determined that long-term levels of the antithyroid antibodies were statistically significantly lower in patients after TT than in patients after ST ($p < 0.05$).

The incidence of complications developing within different surgical strategies used for GD (TT and ST) was comparable while long-term postoperative TSHR-Ab levels were statistically significantly lower in patients after TT compared with patients after ST. It justifies the use of TT for these patients.

Conclusions

The long-term (5 years) postoperative level of TSHR-Ab was statistically significantly lower in the group of patients after TT and made up 1.15 ± 0.13 IU/L (thus corresponding to the normal level).

Total thyroidectomy is an optimal surgical technique and is more appropriate compared with subtotal thyroid gland resection. It should be noted that TT has the same risk of causing complications but no recurrence of thyrotoxicosis.

Author contributions

Study concept and design, data collection and analysis, article writing, review, and final article approval — S. L. Shliakhtych; study concept and design, data collection and analysis, review, and final article approval — V. R. Antoniv.

Declaration of interests

The authors have no conflicts of interest to declare.

Funding. This research paper is a part of research activities carried out by the General Surgery Department No 2 of Bogomolets National Medical University and the Endocrine Surgery Department of Kyiv City Clinical Hospital No 3.

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Результати хірургічного лікування хвороби Грейвса залежно від показників антитиреоїдних антитіл

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Хвороба Грейвса (ХГ) — це спадкове автоімунне захворювання, що характеризується стійкою патологічною гіперсекрецією тиреоїдних гормонів із розвитком синдрому тиреотоксикозу. Частота ХГ у різних регіонах становить від 0,5 до 2,0 %. У 46 % пацієнтів розвивається ендокринна офтальмопатія. Хвороба Грейвса часто є причиною інвалідизації працездатного населення віком до 60 років. Упродовж останніх років поширення ХГ в Україні зросло на 9,9 % — зі 106,2 до 117,9 випадку на 100 тис. населення. Це може бути пов'язано як з поліпшенням діагностики і активним виявленням захворювання, так і зі збільшенням кількості автоімунних уражень щитоподібної залози. Тривають дослідження з профілактики специфічних ускладнень і рецидивів при оперативному лікуванні ХГ.

Мета — порівняти рівні антитіл до рецептора тиреотропного гормону (АТ-РТТГ) у різні строки після хірургічного лікування, а також частоту ранніх та пізніх післяопераційних ускладнень при різному обсязі хірургічного лікування хвороби Грейвса.

Матеріали та методи. Проведено порівняння результатів хірургічного лікування 130 пацієнтів з ХГ (29 чоловіків і 101 жінка віком від 19 до 76 років (середній вік — (44,1 ± 3,2) року), які перебували на лікуванні у Київському центрі ендокринної хірургії в період з 2010 до 2018 р. Тривалість захворювання на момент операції становила від 1 до 30 років (у середньому — (4,6 ± 1,2) року). Пацієнтів рандомізували на дві групи залежно від обсягу хірургічного втручання: у першій (n = 65) проведено тотальну тиреоїдектомію (ТЕ), у другій (n = 65) — субтотальну резекцію щитоподібної залози (СРЩЗ). Проаналізовано тривалість оперативного втручання, кількість ранніх (кровотечі та пошкодження поворотних гортанних нервів) та віддалених результатів операційного втручання (розвиток стійкого гіпотиреозу і рецидивів тиреотоксикозу) залежно від обсягу операції. Також вивчено динаміку зменшення вмісту АТ-РТТГ у різні строки після операції.

Результати. При порівнянні результатів ТЕ та СРЩЗ не виявлено статистично значущої різниці за такими критеріями оперативного втручання, як середня тривалість операції, середній об'єм інтраопераційної крововтрати і середня тривалість післяопераційного стаціонарного лікування. Групи статистично значущо відрізнялися за об'ємом кукси щитоподібної залози, середньою кількістю виділень по дренажу. Отримані результати дають підставу вважати ТЕ оперативним втручанням з меншим ризиком виникнення ускладнень. За кількістю ранніх післяопераційних ускладнень статистично значущої різниці між групами не виявлено ($p > 0,05$). Через 5 років після ТЕ рівень АТ-РТТГ знижувався до референтних значень ((1,15 ± 0,13) МО/л), після СРЩЗ — залишався високим ((5,48 ± 0,42) МО/л; $p < 0,05$).

Висновки. Вважаємо ТЕ порівняно із СРЩЗ оптимальним за об'ємом оперативним втручанням з меншим ризиком виникнення ускладнень з огляду на статистично значущо нижчий рівень АТ-РТТГ у віддалений післяопераційний період.

Ключові слова: антитіла до рецептора тиреотропного гормону, хвороба Грейвса, субтотальна резекція щитоподібної залози, тиреоїдектомія.

FOR CITATION

Shliakhtych SL, Antoniv VR. Results obtained after the surgical treatment of Graves' disease depending on the levels of anti-thyroid antibodies. General Surgery (Ukraine). 2021:1;36-41. http://doi.org/10.30978/GS-2021-1-36.

UDC 616.37-002; 616.37-089; 616-06; 578.834.1
DOI http://doi.org/10.30978/GS-2021-1-42

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

A case report of severe acute pancreatitis with infected necrosis and concomitant Coronavirus Disease-19 (COVID-19): a nosocomial infection or delayed respiratory manifestation of viral disease?

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The association between COVID-19 and acute pancreatitis (AP) has been extensively analyzed in recent research and review papers worldwide. It should be noted that most studies have focused on AP as a COVID-19 complication and/or an extra-pulmonary manifestation of the disease, although the investigation reports on the cases of prior pancreatitis and subsequent COVID-19 infection are limited.

The aim of this case report is to describe the treatment protocol and clinical outcome of a patient with acute necrotizing pancreatitis who developed nosocomial COVID-19..

Case presentation. The data were collected from patient S., a 42-year-old male admitted with AP to the intensive care unit of Kyiv City Clinical Emergency Hospital, in October 2020. This study was reviewed and approved by the local Ethics Committee (Protocol No 25-15-60). The patient signed written informed consent to participate in the study, after having been informed of all relevant aspects that could influence his decision.

The patient, primarily diagnosed with AP, was admitted to the hospital without a PCR test for detecting SARS-CoV-2. 21 days after his admission to the hospital, the patient developed COVID-19. AP progression to severe AP with infected necrosis, the development of systemic inflammatory response syndrome and multiple organ failure necessitated operative pancreatic debridement, which was postponed due to severe acute respiratory failure. Operative pancreatic debridement was performed on the 45th day of hospital stay after the resolution of COVID-19-associated *pneumonia*. The postoperative period was typical for the disease severity and the extent of the surgery, and was complicated by external pancreatic and colonic fistulas. The length of hospital stay for this patient was 115 days which included 20 days of treatment and monitoring in the intensive care unit due to *pneumonia*. He was discharged after clinical symptom improvement.

Conclusions. It is imperative to screen patients presenting with AP for SARS-CoV-2 in order to avoid misdiagnosis and inappropriate treatment strategy. Further detailed investigation of mechanisms of pancreatic injury in patients with SARS-CoV-2 is necessary.

Keywords
Acute necrotizing pancreatitis, SARS-CoV-2, COVID-19.

ARTICLE • Received 2021-10-21 • Received in revised form 2021-10-29

The association between Coronavirus disease 2019 (COVID-19) and acute pancreatitis (AP) is comprehensively presented in numerous case reports, a few case cohort studies and review papers since the onset of the COVID-19 outbreak [4, 5, 7]. It's currently assumed that the causative agent of COVID-19 (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) has a wide range of cellular targets including those in the lungs, kidneys, liver, heart, brain, blood and etc. [19]. The multitarget nature of COVID-19 infection can be primarily explained by the expression of angiotensin-converting enzyme 2 (ACE2) in various organs, since it acts as the receptor to which the SARS-CoV-2 Spike glycoprotein (S) binds to invade the cells [11].

Consequently, COVID-19 can induce numerous extrapulmonary manifestations including gastrointestinal (GI) ones. GI manifestations of COVID-19 most commonly include but are not limited to dysgeusia, nausea, vomiting, diarrhea, and abdominal pain [15]. In the pancreas, SARS-CoV-2 receptive molecules are expressed by exocrine cells, β-cells, as well as pericytes [14]. Most of the studies focus on COVID-19-associated AP [5]. However, the information on the cases of nosocomial COVID-19 in AP patients is scarce [8]. Prognosis of AP course and evaluation of the disease severity in presence of nosocomial COVID-19 are quite complicated, and require the accumulation and analysis of clinical experience. This case report describes the treatment protocol and the clinical outcome of the patient with acute necrotizing pancreatitis and concomitant nosocomial COVID-19.

Case presentation

Herein we report the case of treatment of the patient with AP who developed nosocomial COVID-19. Written informed consent was obtained from the patient and the local Ethics Committee approved the publication of the case (Protocol No 25-15-60). A 42-year-old obese male patient S. with a body mass index (BMI) of 35 kg/m^2 and suspected AP was delivered to the Kyiv City Clinical Emergency Hospital by the medical team of the Center for Emergency Care and Disaster Medicine, Kyiv, on October 17, 2020. On admission, the patient, presenting with pain of 9-hour duration, reported long-term alcohol intake and fatty food consumption prior to seizures. The patient claimed that he didn't have any contact with a COVID-19-positive person as well as any symptoms of viral disease. For these reasons, diagnostics of COVID-19 was not conducted. Physical examination revealed abdominal bloating, sharp pain in the epigastric region, weakened peristalsis,

Table 1. **Laboratory findings throughout the course of the disease**

Parameter	Day 1	Day 66	Day 80	Day 87	Laboratory reference range
Hemoglobin, g/L	181	62	79	95	130—160
Hematocrit, %	54	20	26	31	40—48
RBC count, 10^6/μl	5.4	2.2	2.7	3.2	4.5—5.9
WBC count, 10^3/μl	18.2	6.4	11.3	9.7	3.9—10
PLT count, 10^3/μl	410	198	513	454	180—320
Aspartate aminotransferase (AST), μkat/L	0.48	0.19	0.41	0.56	0.1—0.45
Alanine aminotransferase (ALT), μkat/L	0.44	0.37	0.42	0.45	0.1—0.68
α-amylase (AML), U/L	365.0	39.9	41.0	23.4	12—32
Glucose, mmol/L	30.2	8.7	8.4	10.7	3.3—6.5
Creatinine, μmol/L	190	151	67	83	71—106
Blood urea nitrogen, mmol/L	8.2	2.0	7.3	10.0	2.5—8.3
Total serum protein, g/L	50	54	70	71	60—83
Total bilirubin, μmol/L	30.5	10.5	10.2	12.4	2—21
Direct bilirubin, 0—5 μmol/L	8.0	2.3	1.8	2.9	0—5

and dry tongue. The patient was hemodynamically stable and presented with a heart rate of 112 beats per minute, blood pressure of 158/90 mm Hg, and a temperature of 37.5 °C. Controlled hypertension was reported by the patient as the only comorbidity. The admission laboratory testing showed elevated blood amylase, pronounced leukocytosis, increased total and direct bilirubin (Table 1).

Elevated creatinine level (190 μmol/L) indicated moderate renal failure according to the revised Atlanta classification and Marshall scoring system [3]. Furthermore, the patient was diagnosed with new-onset diabetes mellitus considering an increase in blood glucose to 30.2 μmol/L. Ultrasound of the abdomen showed enlarged and edematous pancreas, as well as free fluid in the abdominal cavity. A chest X-ray on admission didn't not exclude moderate left lower lobe pneumonia and left-sided hydrothorax.

According to the local protocol, the patient was admitted to the intensive care unit, where his condition was managed using the «rule of four catheters» (a catheter for epidural anesthesia, the placement of an enteral feeding probe beyond the ligament of Treitz, the central vein catheterization, the programmed laparocentesis with evacuation of 250 ml of fluid) [18]. In the intensive care unit, the patient underwent fluid resuscitation with balanced isotonic crystalloid solutions (5.6 L/24 h), epidural analgesia (bupivocaine 3 ml every 3 hours) with blood pressure control and enteral tube feeding (25—35 % of the total fluid volume) as well as received pantoprazole 120 mg/24 h,, insulin 10 U/24h, antibiotic prophylaxis with leflocin (500 mg. i.v., twice daily), metrid (1 g, three times a day), and ceftriaxone (1 g i.v., twice daily) on the third day of hospital stay (October 19, 2020).

The patient was transferred to the surgical department on the 4th day from the onset of the disease (October 20, 2020). Ultrasound monitoring, which was carried out on day 7 (October 23, 2020), revealed fluid accumulation in the omental bursa up to 500 ml. Consequently, its puncture and drainage were performed using a catheter Pig tail 9 Fr. On day 17 (November 2, 2020), the fluid drainage was carried out and 600ml of fluid were removed from the left paracolic retroperitoneal space. On day 19 of the disease (November 5, 2020), spiral computed tomography (SCT) revealed destructive pancreatitis with infiltration of parapancreatic tissue spreading to the omental bursa, spleen gate, duodenum and stomach as well as the root of the small-bowel mesentery.

On day 20 (November 6, 2020), the patient's condition deteriorated due to progressive respiratory failure (SpO2 86 %). The patient tested positive for COVID-19. A chest X-ray revealed bilateral polysegmental pneumonia (Fig. 1). On day 21 (November 7, 2020), progressive respiratory failure was observed (SpO2 82 %), and endotracheal intubation with mechanical ventilation was performed. On day 24 (November 10, 2020), the patient underwent extubation followed by humidified oxygen insufflation through a face mask and nasal catheters. On day 27 (November 13, 2020), the patient was transferred to the surgical department as well as insufflated with humidified oxygen (4—10 L/min) due to his oxygen-dependence.

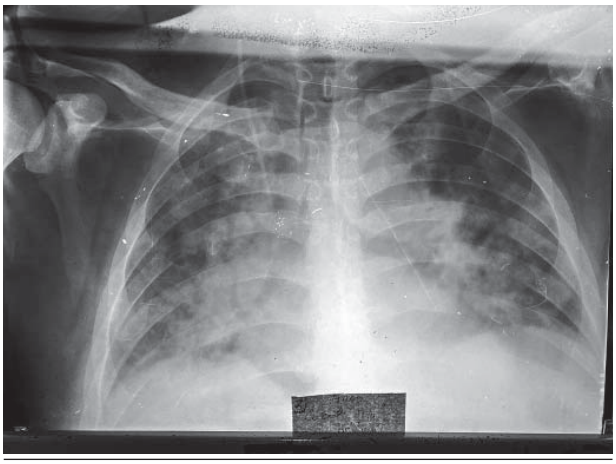

Figure 1. **Chest X-ray image of the patient S. with AP after the PCR-confirmed COVID-19 infection on the 20th day of hospital stay**

The objective examination (purulent discharge through drainage) and signs of SIRS (temperature > 38 °C; heart rate > 90 beats/min; WBC

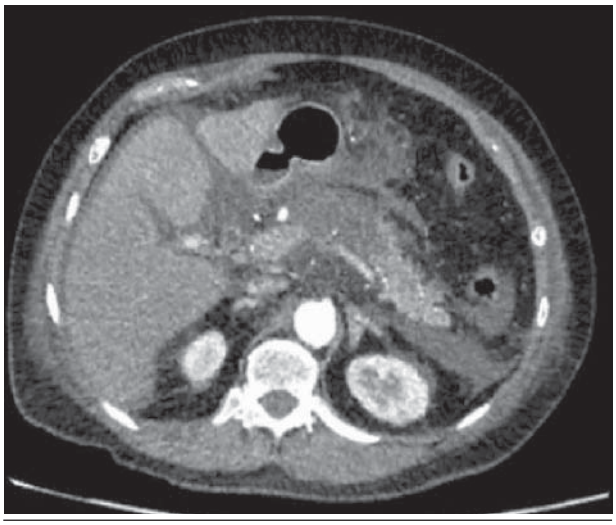

Figure 2. **Abdominal SCT scan showing destructive pancreatitis with parapancreatic infiltrate, formation of limited peritoneal fluid accumulations, mesenteric and peritoneal lymphadenopathy, and bilateral hydrothorax**

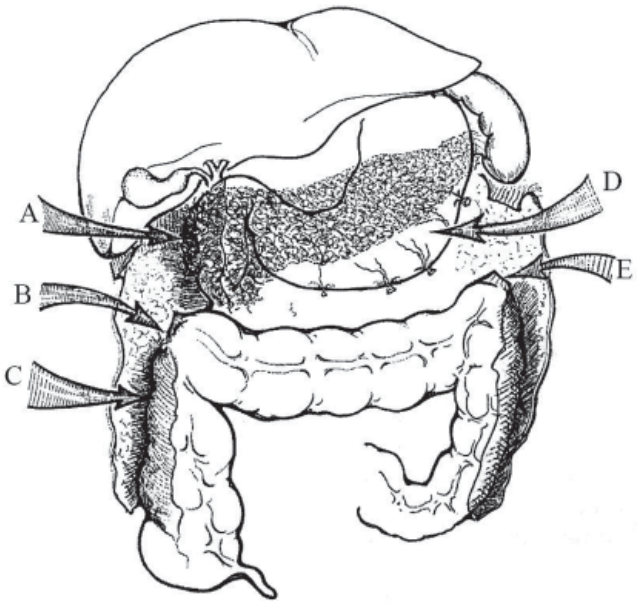

Figure 3. **Schematic representation of the operative decompression of the retroperitoneal spaces:** A — hepatic flexure of colon; B — right paracolic retroperitoneal space; C — the tail area of the pancreas; D — splenic flexure of the colon; E — left paracolic retroperitoneal space

count > $12 \cdot 10^9$/L) necessitated surgery, but it was postponed due to signs of respiratory failure.

SCT performed on day 40 (November 26, 2020) revealed destructive pancreatitis with parapancreatic infiltration, formation of limited peritoneal fluid accumulations, mesenteric and peritoneal lymphadenopathy, and bilateral hydrothorax (Fig. 2).

On day 45 of the disease (December 1, 2020), open operative pancreatic debridement (OPD) was performed. Several areas of necrotic lesions were identified, including paraduodenal and right lateral canal area, parapancreatic area, root of the small-bowel mesentery and left paracolic retroperitoneal space. In this case, the Kocher mobilization of the duodenum and hepatic flexure of colon were performed along with the dissection of splenic-colon and colon-diaphragmatic ligaments, parietal peritoneum of the left lateral canal outward from the descending part of the colon and mobilization of splenic flexure (Fig. 3).

The postoperative period was typical for the disease severity and the extent of the surgery, and was complicated by external pancreatic and colonic fistulas.

Serum level of α-amylase and WBC count were progressively decreasing during post-surgery period, and reached normal value on day 87 (see Table 1). Glucose level was also decreasing, but exceeded the reference range. Along with mild elevation of AST level and moderately increased serum creatinine, it indicated ongoing diabetes. The patient was discharged after clinical symptom improvement.

Discussion

Increasing number of cases of coexistence of AP and COVID-19 necessitate studying clinical experience on this issue. In most cases, AP is regarded as the secondary or even primary presentation of COVID-19 considering the tropism of SARS-CoV-2 to different tissues including pancreatic and parapancreatic ones [11, 19]. It presumably causes GI symptoms of COVID-19, which mimic typical AP manifestations. In all these cases, patients have ongoing COVID-19 infection, confirmed by the results of PCR-test and CXR/CT, at the time of AP onset. The most common features of AP are the absence of similar attacks in the past medical history, most often the absence of any other etiological factors that could cause the development of the disease (excessive alcohol and fatty food consumption, trauma, gallstone migration and etc.) as well as mild course of the disease (results of CT) with moderate abdominal pain [2, 10, 12, 16]. In addition, AP can develop as the complication of the underlying COVID-19. At the time of AP onset, PCR-test can be negative and patients can be presented with resolved pneumonia, therefore, AP can be an early presentation of COVID-19-associated multisystem inflammatory syndrome [1, 17].

In our case, a different picture of the AP and COVID-19 association was observed when typical symptoms of coronavirus infection were secondary to AP and developed in presence of pancreatitis symptoms. Similarity of the clinical pattern of these diseases significantly complicates diagnosis in the absence of molecular detection of the pathogen. GI symptoms are widely reported for patients with COVID-19. SIRS signs are typical for both pathologies. Moderate respiratory failure in AP patients could mimic mild COVID-19 course. Even new-onset diabetes mellitus, which is noted as the commonest comorbidity in COVID-19 [13], is also inherent to AP [20].

Our assumption concerning the nosocomial origin of COVID-19 was based on the course of the inflammatory component of AP. It is well documented that SIRS lasts about 14 days in patients with AP, gradually leading to compensatory systemic anti-inflammatory syndrome (CARS) with compromising immune system patrolling function and increased risk of infection [6]. Nevertheless, the presence of COVID-19 cannot be excluded

on admission, since according to Galanopoulos et al., 2020, patients, presenting exclusively with GI symptoms, have delayed diagnosis of COVID-19 and in their case the first respiratory symptoms appear later [9]. Therefore, it can be assumed that viral infection of the pancreas along with excessive alcohol and fatty food consumption reported by the patient on admission triggered pancreatitis. COVID-19 diagnostics on admission could facilitate decision making and prediction of the clinical course of the disease.

Conclusions

Although there is no satisfactory evidence showing that COVID-19 can cause AP or negatively influence prognosis, we consider that it is mandatory to screen patients presenting with AP for SARS-CoV-2 in order to avoid misdiagnosis and inappropriate treatment strategy. A deep insight into the mechanisms of SARS-CoV-2 pancreatic injury is needed for exploiting a causal relation between these two entities in differential diagnostics.

Acknowledgements

The authors are very grateful to the staff of Kyiv City Clinical Emergency Hospital recruited into this study.

Declaration of interests

The authors declare that they have no conflicts of interest.

Funding. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and written informed consents statements

The project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects of Kyiv City Clinical Emergency Hospital (Kyiv, Ukraine), based on the Declaration of Helsinki. Patient gave his written informed consent prior to study inclusion.

Author contributions

Y. Susak: chief surgeon, performed the OPD on patient who was included in this study; O. Lobanova: data interpretation; O. Tkachenko: supervisor, design of the study; L. Skivka: drafting the manuscript, data analysis.

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Повідомлення про випадок тяжкого гострого панкреатиту з інфікованим некрозом та супутньою коронавірусною хворобою-19 (COVID-19): внутрішньолікарняна інфекція чи відтермінований респіраторний вияв вірусної хвороби?

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Взаємозв'язок між коронавірусною хворобою-19 (COVID-19) та гострим панкреатитом (ГП) широко обговорюється у дослідницьких та оглядових публікаціях. У більшості праць ГП розглядають як ускладнення COVID-19 та/або позалегеневий вияв захворювання. Значно менше уваги приділяється випадкам панкреатиту з наступним розвитком COVID-19.

Метою цього звіту є опис протоколу та клінічних результатів лікування пацієнта з гострим некротичним панкреатитом, у якого розвинулася внутрішньолікарняна COVID-19.

Клінічний випадок. Пацієнт С. (чоловік, 42 роки) госпіталізований з попереднім діагнозом ГП у відділення інтенсивної терапії Київської міської клінічної лікарні швидкої допомоги у жовтні 2020 р. Протокол дослідження було розглянуто та схвалено місцевим комітетом з біоетики (протокол № 25-15-60). Письмова інформована згода отримана від пацієнта після пояснення змісту дослідження.

У пацієнта з первинним діагнозом ГП, якому на момент госпіталізації не проводили виявлення за допомогою полімеразної ланцюгової реакції коронавірусу тяжкого гострого респіраторного синдрому-2 (Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)), через 21 день після надходження до лікарні було діагностовано COVID-19. Прогресування ГП (до тяжкої форми з інфікованим некрозом, синдромом системної запальної реакції та поліорганною недостатністю) потребувало панкреатонекрсеквестректомії, яку було відкладено через тяжку гостру дихальну недостатність. Операцію проведено на 45-ту добу перебування у лікарні після усунення пневмонії, пов'язаної з COVID-19. Післяопераційний період перебігав відповідно до тяжкості захворювання та об'єму операції і був ускладнений зовнішніми панкреатичною та товстокишковою норицями. Пацієнт перебував у лікарні впродовж 115 діб, з них 20 діб був під наглядом у відділенні інтенсивної терапії, призначеному для випадків пневмонії. Він був виписаний після поліпшення симптомів у задовільному стані.

Висновки. На момент госпіталізації пацієнтів з попереднім діагнозом ГП слід проводити скринінг на наявність SARS-CoV-2 з метою уникнення помилкового діагнозу та оптимізації стратегії лікування, з огляду на подібність симптомокомплексу ГП і абдомінальних симптомів позалегеневої маніфестації COVID-19. Глибокого вивчення у контексті існуючої коморбідності потребують механізми ураження підшлункової залози SARS-CoV-2.

Ключові слова: гострий некротичний панкреатит, SARS-CoV-2, COVID-19.

FOR CITATION

Susak Y, Tkachenko O, Lobanova O, Skivka L. A case report of severe acute pancreatitis with infected necrosis and concomitant Coronavirus Disease-19 (COVID-19): a nosocomial infection or delayed respiratory manifestation of viral disease? General Surgery (Ukraine). 2021:1;42-47. http://doi.org/10.30978/GS-2021-1-42.

UDC 616.131:611.146:616-005.756.6:616.31-001.45
DOI http://doi.org/10.30978/GS-2021-1-48

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Associated projectile inferior vena cava wound with subsequent pulmonary artery missile embolization: a case report and literature review

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A rare and unpredictable complication of firearm and missile injuries is projectile embolism. With only a few cases described in the literature, bullet embolism may become a diagnostic challenge for emergency physicians and military surgeons. Bullet embolization is a rare phenomenon, but the complications can be devastating.

Case presentation. A 34-year-old man sustained a severe complex abdominoskeletal mine-blast injury with damage to the hollow organs (duodenum and transverse colon), inferior vena cava and both low extremities. The internal hemorrhage was stopped by phleborrhaphy. The wounds of the duodenum and large intestine were sutured, and gunshot fractures of both anticnemions were stabilized by extrafocal osteosynthesis. The whole-body CT showed that there was a projectile embolus into the branch of the right mid-lobe pulmonary artery. No clinical manifestations of pulmonary artery embolism were observed in the patient. After surgery, he developed multiple necrosis and transverse colon perforations that resulted in fecal peritonitis. The suture line leakage that caused the formation of a duodenal fistula and postoperative wound infection were also detected. The complications were managed by multiple reoperations. The attempts of endovascular bullet extraction weren't undertaken due to severe concomitant injuries, complications and asymptomatic clinical course of pulmonary artery projectile embolism. Open surgery retrieval of the embolus was successfully performed on the 80th day after injury. The patient was discharged from the hospital in good condition on the 168th day after the missile wound.

Conclusions. Patients with missile wounds and no exit gunshot perforation should be examined using the whole-body CT for determining possible migration of a projectile with the blood flow. Patients with asymptomatic pulmonary artery embolism should be managed nonoperatively. In case of symptomatic pulmonary artery projectile embolism, it is reasonable to consider the possibility of open thoracic surgery.

Keywords
missile wound, inferior vena cava, pulmonary artery, venous missile embolism.

ARTICLE • Received 2021-10-01 • Received in revised form 2021-10-04

The hybrid war of Russia against Ukraine has been ongoing in certain districts of Donetsk and Luhansk oblasts within the Donbas area since 2014 and this armed conflict is officially entitled as an antiterroristic operation (ATO) by Ukrainian government [16]. The pro-Russia separatists use various types of weapons against Armed Forces of Ukraine, for instance, artillery, multiple launch rocket systems, and such explosive devices as land mines or improvised explosive devices (IED). The administration of high-energy weapons is associated with severe injury of military personnel, which frequently results in thoraco-abdominal traumas or upper/lower extremity amputations.

A rare complication of combat injuries is arterial or venous embolism caused by bullet or fragmentation of explosive devices, which is described in case report studies [6, 7, 10]. IED fragment embolism

may be a cause of death due to its association with limb-threatening ischemia, sepsis, endocarditis, cardiac valves insufficiency, pulmonary embolism, and stroke [31]. Furthermore, diagnosis of arterial embolism can be challenging due to the migration of the fragment, rare presentation and diagnostic difficulties.

According to the previously published case reports, X-ray and computed tomography (CT) are used for detection of bullet emboli into blood vessels following gunshot injuries in non-war situations. This type of embolism is rare and may be suspected in patients with perforating injuries or bleeding into the peritoneal/retroperitoneal space. Nevertheless, the possibility of bullet or metal fragment embolism cannot be ignored [14, 23]. The previously published reports suggest the following criteria that indicate a high risk of projectile embolism: the changing shrapnel position in the subsequent X-ray images referred to as «roaming bullet» phenomenon; absence of an exit wound [40]; there are more entrance wounds than exit wounds [10]; the actual location of the embolic metal fragment, as seen on X-ray or CT, that does not correspond with the location of the bullet wound channel [6, 7, 23, 31]. If the above-mentioned diagnostic signs are observed in a patient after gunshot injury, the whole-body CT and angiography are justified for specifying a projectile position and evaluation of distal circulation [7, 10, 40].

The aim of this study was to report a clinical case of a combat patient who was injured in an armed conflict in eastern Ukraine, underwent the whole-body CT scan and was diagnosed with pulmonary artery embolism caused by a fragment after a booby trap explosion. Furthermore, the study was aimed to review the existing data suggested by previously published case reports on the clinical features of blood vessel embolism caused by bullet or projectile fragments.

Case presentation

On May 30, 2017, a 34-year-old male received a complex abdominoskeletal mine blast trauma at approximately 09 : 10 am during a combat mission in the area of the battle conflict zone in eastern Ukraine (Donetsk region, Leninske settlement). Aspects of trauma — mine explosion (tripwire trap). Type of trauma — penetrating blind wound of the abdomen with the injury to the colon and duodenum, as well as marginal injury of the inferior vena cava. Multiple gunshot missile wounds of both lower extremities with the gunshot fractures of the tibia and fibula in the upper third of the left shin and in the lower third of the right shin with the displacement of fragments; injury to the right posterior tibial artery. A gunshot missile perforating wound of soft tissues of the right hand.

Medical emergency treatment was provided on the spot by the medical personnel of the unit: a military emergency tourniquet was placed on the right lower extremity; one dose of narcotic pain medication (Butarphanolum 2 mg), an antibiotic (Doxycycline 100 mg) and tetanus toxoid (Anatoxin tetanus 0.5 ml) were administered intramuscularly; aseptic dressing was applied to the wounds of the abdomen and extremities; the transport immobilization of both lower extremities was carried out using the ladder splint. The wounded casualty was urgently evacuated by ambulance to the nearest stage of providing qualified medical assistance.

Qualified surgical treatment was provided in the Central district hospital of Toretsk city, reinforced by specialists in military medicine. The wounded casualty was admitted to the hospital within 55 minutes after injury, according to the principle of the «golden hour». At the time of admission to the stage of qualified surgical care, the patient had absolute signs of a penetrating wound of the abdominal cavity (the dressing was impregnated with intestinal contents and blood) and a clinical picture of the continuing internal bleeding with severe hemorrhagic shock. Consequently, the wounded casualty underwent emergency laparotomy without preoperative preparation. During the operation, there were found out such injuries as: a through and through missile wound of the transverse colon with torn edges, a perforating missile through and through wound of the horizontal part of the duodenum (the 3rd part), a focus of primary traumatic necrosis of the head of the pancreas, diffuse fecal peritonitis in reactive phase; tense retroperitoneal hematoma of large size with severe blood loss (approximate volume of blood loss was 1800 ml). The disclosure, evacuation and revision of the retroperitoneal hematoma was performed, its source was revealed and included a marginal wound of the infrarenal part of the inferior vena cava. The first stage was placing a vascular suture on the wound of the inferior vena cava to achieve persistent hemostasis. Intensive transfusion of blood preparations (3 doses of erythrocyte mass, 2 doses of fresh frozen plasma) and infusion therapy with colloids and crystalloids were started for arresting the phenomena of severe hemorrhagic shock caused by massive plasmic-blood loss. Taking into account the critical condition of the wounded casualty, the decision to perform minor surgery for small and large intestinal wounds was made. According to the damage-control tactics, the surgical procedure

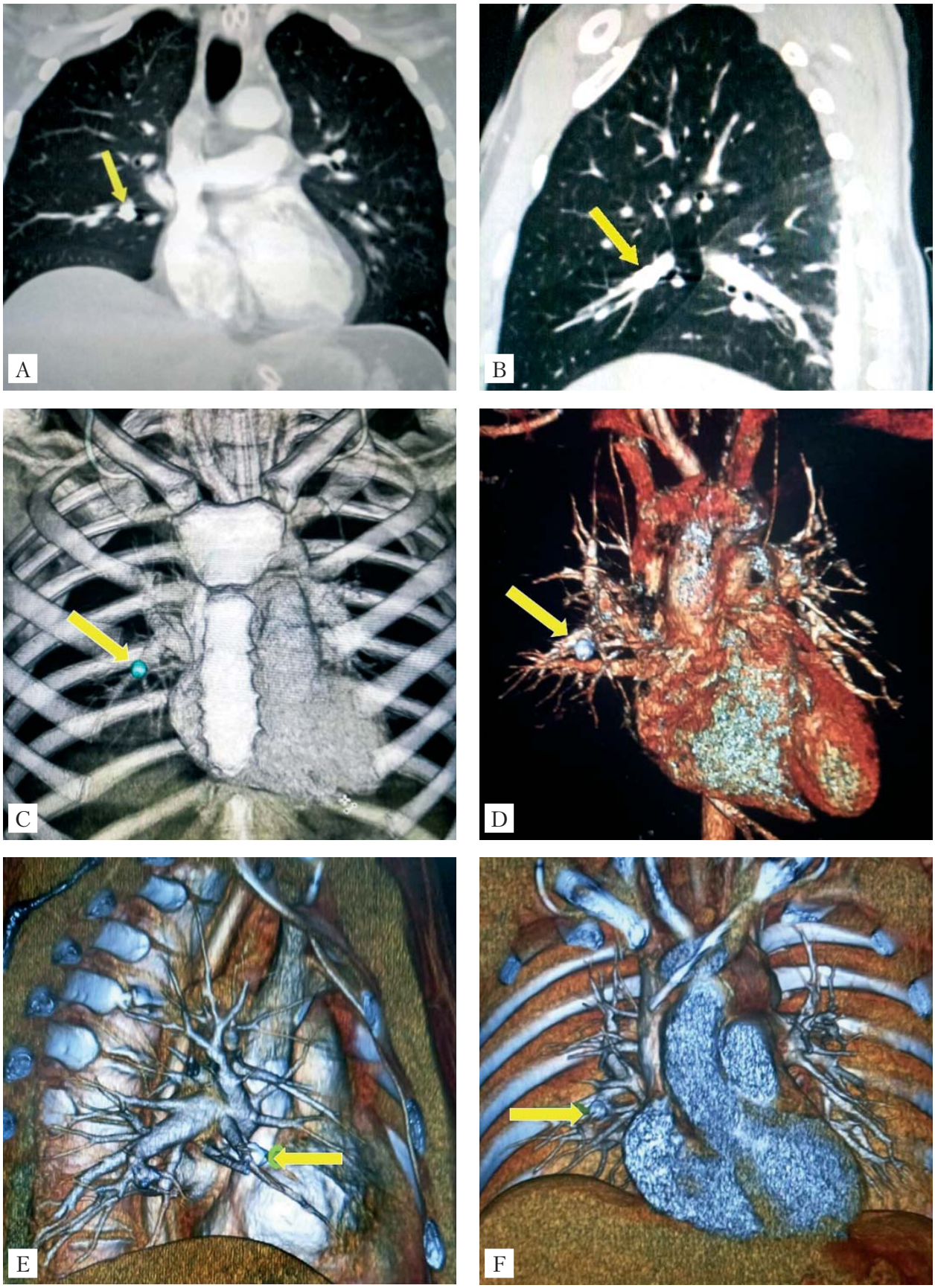

Figure 1. **Spiral computed tomography scan of the wounded casualty on the 3rd day after the injury:**
A, B — frontal and sagittal reconstruction of the image; C — 3D-reconstruction; D — computed tomography angiography; E, F — computed tomography angiography with 3D image reconstruction.
The arrow indicates the location of the missile in the branch of the right mid-lobe pulmonary artery

included placing a three-row suture on the wound of the transverse colon, placing a double-row suture on the wound of the horizontal part of the duodenum, insertion of nasojejunal tubes, drainage of the abdominal cavity (to the sites of the sutures on the duodenum, inferior vena cava and small pelvis), and laparotomy wound suturing. Resection of necrotic foci in the head of the pancreas was not performed. In order to stabilize the systemic hemodynamics after the abdominal stage of the operation, a 30-minute pause was made for intensive infusion therapy. After stabilization of hemodynamics, operation on the lower extremities was carried out. After removing the military emergency tourniquet, bleeding from the right tibial artery was revealed, but there were no signs of critical limb ischemia. Due to the extremely severe condition of the patient, the multiple nature of the lesions and the absence of signs of critical limb ischemia, and according to the damage-control tactics, a decision was made to perform final hemostasis on the right lower extremity using ligation of the right posterior tibial artery, which is the least traumatic type of surgery. In order to stabilize the sites of gunshot fractures of the bones of the left tibia, extra-focal metalosteosynthesis was performed with a rod external fixation device. As the final evaluation of the right shin viability after ligation of the posterior tibial artery was impossible, metalosteosynthesis on the right limb was not performed. On June 31, 2017 (the 2nd day after injury), the patient was evacuated by air transport to the stage of specialized surgical treatment.

Specialized surgical treatment was provided to the wounded casualty in the Military Medical Clinical Center of the North Region (Kharkiv). Upon admission, the patient underwent ultrasonography of the abdominal and pleural cavities, and the spiral computed tomography (SCT) of the cranial, thoracic and abdominal cavities. According to ultrasonography, the inferior vena cava was not dilated, the blood flow was retained, and there was a small amount of fluid in the right paranephric fatty tissue. According to the SCT, there were no signs of retroperitoneal hematoma; a foreign body of metallic density of 9.5 × 6.5 mm was detected in the branch of the right mid-lobe pulmonary artery (Fig. 1). No wound holes were detected on the chest and the diaphragm, so it was assumed that the missile migrated from the inferior vena cava to the pulmonary artery after surgery. Taking into consideration the absence of clinical manifestations of the pulmonary artery missile embolism, severe patient's condition and the presence of severe combined abdominoskeletal trauma, no attempt of X-ray endovascular removal of the missile was made.

Due to the viability of the tissues of the right lower extremity after ligation of the posterior tibial artery on the 2nd day after injury, repeated surgical treatment of the secondary necrosis foci of both extremities was performed and fixation of the bones of the right shin with a rod external fixation device was carried out.

The patient was provided with daily changes of the wound dressing, infusion detoxification, antibacterial therapy (Ceftriaxone 4 g/day, Metronidazole

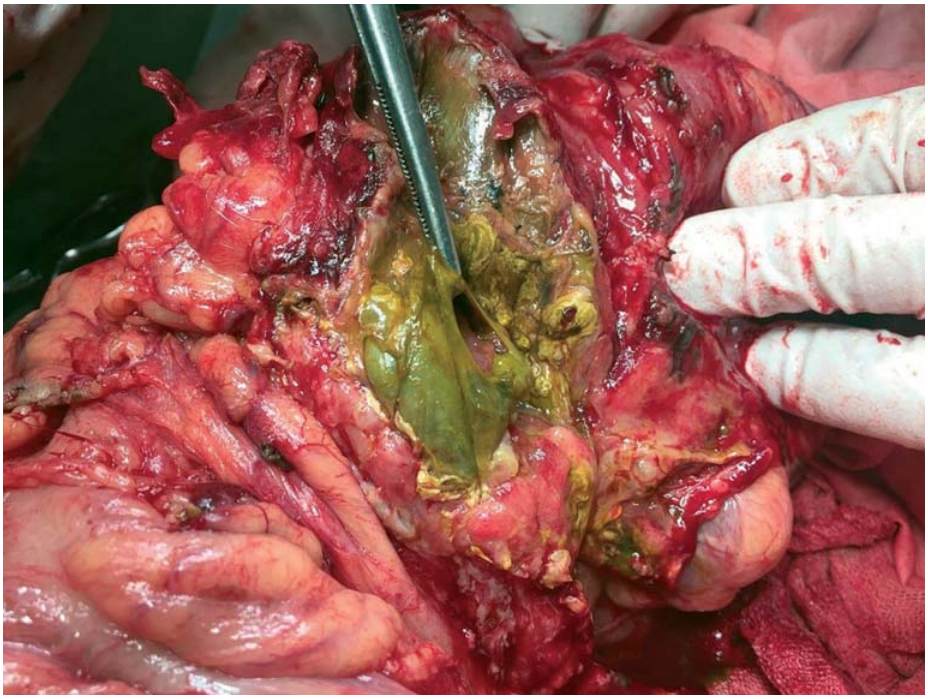

Figure 2. **Intraoperative photo on the 9th day after injury. A zone of necrosis and perforation (indicated by an arrow) at the suturing site of the perforating wound of the transverse colon, local limited fecal peritonitis**

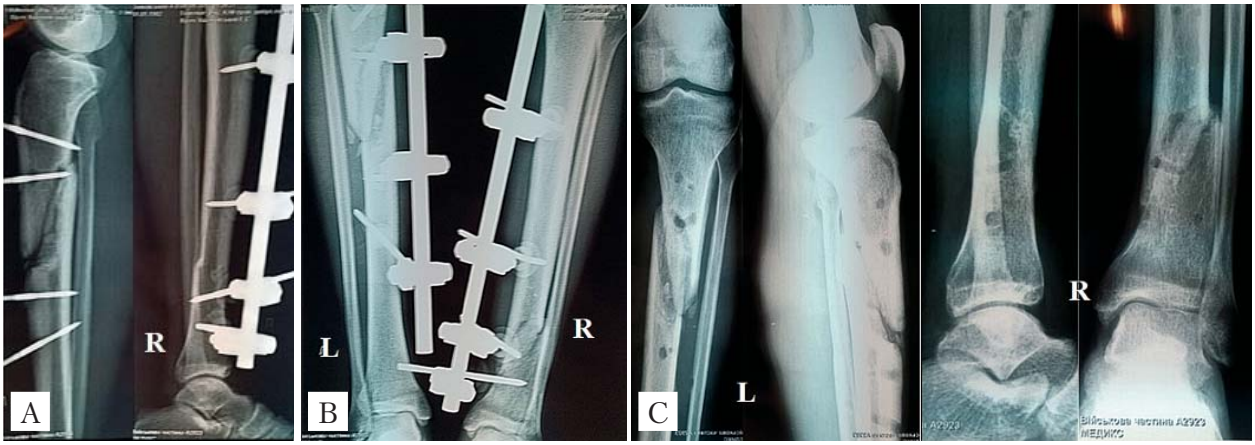

Figure 3. **Dynamics of reparation of the gunshot fractures of the bones of the upper third of the left shin and the lower third of the right shin, metal osteosynthesis by rod external fixation devices:** A — the 102nd day after injury; B — the 154th day after injury; C — the 168th day after injury, the external fixation devices were dismantled, and the patient was discharged from the hospital)

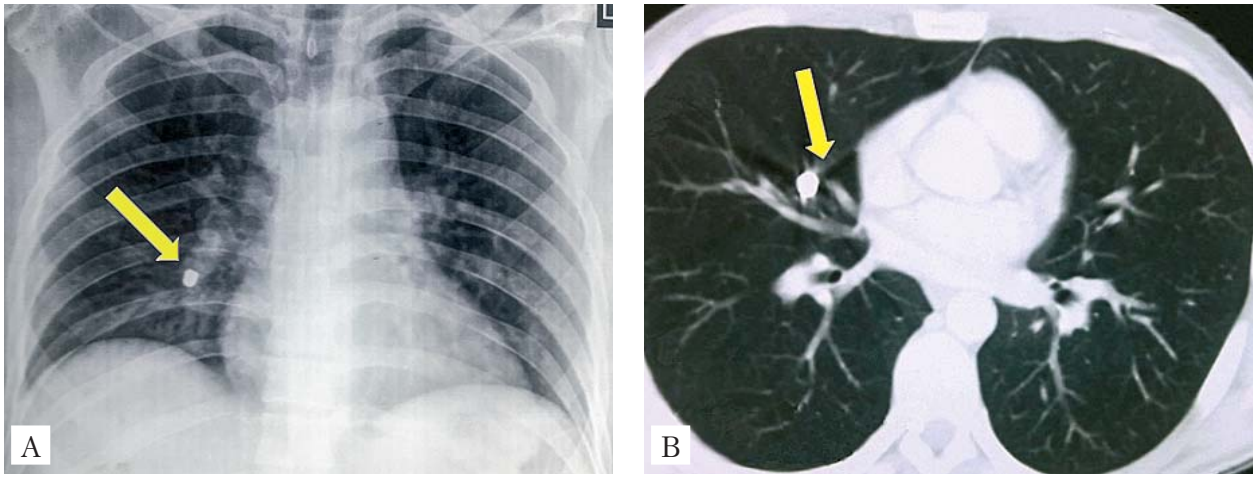

Figure 4. **The position of the missile-embolus in the right mid-lobe pulmonary artery on the 63th days after injury:** A — chest X-ray; B — SCT of the lungs with axial reconstruction of the image. The arrow indicates the position of the missile

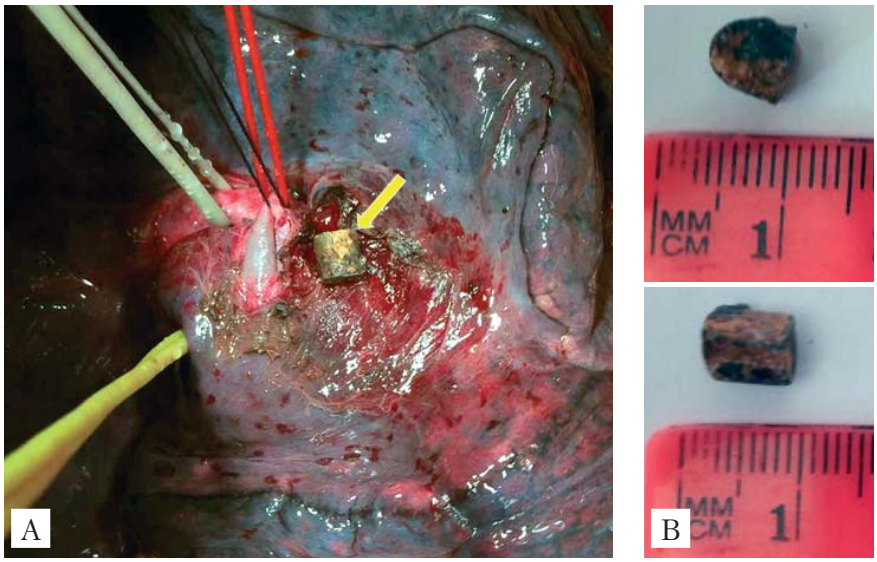

Figure 5. **Intraoperative photo of the missile-embolus removal from the right mid-lobe pulmonary artery (A), and removed missile-embolus (B).** White holder — the trunk of the right pulmonary artery after the origin of the lower-lobe artery; red holder — right mid-lobe pulmonary artery; the dark navy holder is a branch of the right mid-lobe artery to the medial segment (thrombosed); yellow holder — medium-lobe pulmonary vein; the arrow indicates the missile extracted from the lumen of the vessel

1 g/day), parenteral nutrition, supporting medication (Pantoprazole 40 mg/day, Metoclopramide hydrochloride 20 mg/day, Drotaverine hydrochloride 80 mg/day, Enoxaparin sodium 80 mg/day, iron preparations 200 mg/day), transfusion of the same group erythrocyte mass (2 doses), fresh-frozen plasma, albumin (20 g/day), infusion and vitamin therapy (B_1, B_{12}), and physiotherapy.

In the course of the treatment, the patient's condition remained severe stable, the wound process on the lower extremities proceeded according to the nature of the primary lesion. On the 3rd day after injury, enteral feeding was started through the inserted nasojejunaltube, and the drains were removed from the suture site of the inferior vena cava and small pelvis.

On the 8th day after injury, bile discharge through the drainage was detected at the suturing site of the horizontal part of the duodenum. The patient underwent SCT of the abdomen with double contrast. In the native phase, contrasts were found in front of the descending part of the duodenum with dimensions of 6 × 5 × 6 mm without clear boundaries (contrast output from the bowel lumen). A limited fluid cluster (32 × 38 × 34 mm) with air bubbles without clear boundaries was found out (intra-abdominal abscess was suspected) in the same region.

On the 9th day after injury, due to the developed complication that required a long-term highly specialized treatment, the patient was transported by car to the National Military Medical Clinical Center of the Ministry of Defense (Kyiv) for further surgical treatment.

On the 9th day after injury, the patient underwent relaparotomy. In the right upper quadrant of the abdominal cavity, an infiltrate was revised. During its separation, about 50 ml of fecal content was released from the perforation zone of the large necrosis areas in the transverse colon (25 × 30 mm and 15 × 40 mm) at the suturing site of the perforating gunshot wound. Necrosis was probably caused by secondary irreversible changes in the zone of molecular shock resulting from the missile wound. After sanation of the fecal content, a partial suture line leak, along with the pancreatic juice and bile outflow, was also revealed (Fig. 2).

Considering the intraoperative findings, the leaking site in the duodenum was sutured; right hemicolectomy and side-to-side ileotransverse anastomosis were performed. Taking into account the presence of local peritonitis, post-traumatic pancreatitis associated with an injury to the pancreatic head, as well as pancreatic necrosis, the decision was made to disconnect the stomach and the sutured zone of the duodenum from the passage of food.

Therefore, anantecolic gastroenteroanastomosis with Braun anastomosis was imposed, machine stitches were placed on the antral part of the stomach, and a feeding tube was inserted into the efferent jejunal loop of Braun anastomosis. For the purpose of biliary decompression, ultrasound-guided transhepatic cholecystostoma was applied in the right upper quadrant. There were 4 drain tubes in the abdominal cavity (right iliac region, small pelvis, suturing site of the duodenum and gastroenteroanastomosis). The laparotomic wound was sutured.

Massive soft tissue wounds of the lower extremities were treated by repeated surgical procedures, accompanied by the installation of a VAC system with its reassembly within 3—4 days and excision of the soft tissues affected by secondary necrosis. On the 5th day after relaparotomy, suppuration of the laparotomic wound occurred and had to be managed by secondary surgical treatment. Furthermore, the post-traumatic and postoperative period was complicated by right-sided upper-lobe nosocomial *pneumonia* and nonspecific reactive hepatitis, which were corrected with medications.

In the postoperative period, the patient received Doripenem monohydrate 1.5 g/day, Gatifloxacin 400 mg/day, Fluconazole 100 mg/day, Nadroparin calcium 2850 IU, Pantoprazole 40 mg/day, epidural block, enzymes, physiotherapy, and enteral feeding. The bile discharge (daily production of 100—120 ml) was noted as a consequence of the repeated suture line leak at the site of the duodenum on the 2nd day after relaparotomy, and an external duodenal fistula formed. Due to the gastric disconnection and biliary decompression via the cholecystostoma, the volume of the discharge from the duodenal fistula gradually decreased. On the 18th day after imposition of the gastroenteroanastomosis, bile outflow from the fistula was 40—50 ml, the drainage tube was removed, and the fistula healed on the 29th day after the duodenum was disconnected from the food passage.

On the 52nd day after injury, the patient was transferred to the stage of rehabilitation treatment as his general condition was satisfactory.

Rehabilitation treatment was conducted in the Military Medical Clinical Center of Occupational Pathology of Personnel (Irpin). The patient was prescribed and provided with physiotherapy, exercise therapy, massage, change of dressings, and symptomatic medications for multi-fragment gunshot fractures of both shins. There was observed a sluggish course of the bone callus formation at the fracture sites (Fig. 3*A*, *B*).

Due to the fact that the presence of a missile in the right mid-lobe pulmonary artery had no clinical

manifestations and the patient suffered from bullous lung disease of the upper lobe of the same lung, the decision was made to perform open thoracic surgery after the completion of the rehabilitation course. 2.5 months after injury, the possibility of endovascular projectile extraction was not considered as the fragment was firmly lodged in the vessel wall. In addition, the patient had an indication for resection of the same lung due to the diagnosed bullous lung disease with a high risk of spontaneous pneumothorax.

The patient was transferred to the clinic of thoracic surgery of the National Military Medical Clinical Center (Kyiv), where the preoperative examination was performed. According to the results of chest X-ray and computed tomography, the position of the missile-embolus in the right mid-lobe pulmonary artery did not change (Fig. 4).

On the 80th day after injury, the patient underwent right-sided thoracotomy in the 5th intercostal space. During palpation of the right lung, a dense foreign body, measuring approximately 10 mm in diameter, was revealed in the basal region of the middle lobe. The mediastinal pleura was incised, the branches of the right upper pulmonary vein were identified, the right pulmonary artery and the mid-lobe artery were taken by the holders (Fig. 5*A*). During further examination, a foreign body was detected in the lumen of the branch of the right mid-lobe artery of the medial segment (immediately after the bifurcation of the lobar artery). Above the foreign body, the wall of the vessel was opened and a metal missile with dimensions of 8 × 6 mm (Fig. 5*B*) was discovered. It lodged firmly in the vessel wall (the form of the missile-embolus was similar to a piece of metal wire, which is used in the production of anti-personnel mines for the maximum crippling effect). The distal lumen of the artery was thrombosed, whereas the blood supply to the middle lobe of the right lung and its aeration were preserved due to the collateral blood flow. The missile bed was washed with antiseptic; the proximal and distal ends of the vessel were ligated. An atypical resection of the upper lobe of the right lung was performed in response to the presence of the bulls up to 15 mm in the upper lobe of the right lung.

The postoperative period was uneventful. Ciprofloxacin (600 mg/day), ertapenem (1g/day), amikacin sulfate (1 g/day) were administered. The patient was provided with change of dressings, physiotherapy, and exercise therapy. The patient was transferred to the stage of rehabilitation treatment. Bone fractures of both extremities were consolidated, external fixation devices were dismantled on the 168th day after injury (Fig. 3*C*). The patient was discharged from the hospital in a satisfactory condition and then he was medically retired from the military service.

Discussion

History. The first case of intravascular foreign body emboli in a 10-year-old boy was reported by Thomas Davis in 1834, and describes venous embolization of a wooden projectile to the right ventricle [10, 22, 41]. The incidence of bullet embolization is very low, with fewer than 200 cases reported [6, 7, 10, 26]. With the exception of an institutional series of 28 cases presented by Mattox et al. in 1979 [22], almost all cases are presented as single case reports.

Epidemiology. A review of 7500 gunshot wounds during the Vietnam War demonstrated a 0.3 % incidence of bullet embolism [10, 22, 31]. The incidence of missile embolization after penetrating injury was reported to be 1.1 % in the Afghanistan and Iraq Wars (of 346 casualties surveyed) [2, 31, 33]. The incidence of bullet embolization in the civilian setting is unknown, but it could be higher because of the lower velocity weapons with lower kinetic energy found in the civilian setting [31].

Pathogenesis. The scenario for a bullet embolism is set up when a low-velocity projectile contains the amount of kinetic energy enough for the initial tissue penetration so that it may traverse only one wall of a vessel, and then gets trapped within the lumen. Commonly, a bullet embolism occurs mostly with [1, 3, 7, 40]:

- small-caliber guns;
- relatively low-powered projectiles, such as BB guns [7], and airgun pellets [4];
- shotgun ammunition, which scatters multiple small metallic pellets.
- According to the clinical reports, the following conditions, which influence the migration of an intravascular foreign body, can be marked:
- missile size [10];
- hydrostatic pressure from blood flow [1, 7, 27];
- gravity [1, 27];
- patient body position [10, 27];
- vascular anatomy [7, 40];
- muscular and respiratory movement [1, 10].

In the presented case report, a soldier suffered from a missile wound with an injury to the inferior vena cava caused by a projectile. The projectile was a piece of a metal wire, which is usually used for additional filling of anti-personnel landmines to achieve the maximum crippling effect and invalidization of those who fall into a tripwire trap. The cylindrical shape of the projectile caused a complete obturation of the pulmonary vein branch and led to its thrombosis. The missile embolism became possible in the presented case because the projectile lost a great amount of its initial kinetic energy while passing through the anterior abdominal wall and the walls of the large intestine and duodenum. Finally, the shrapnel broke

through one wall of the inferior vena cava and got into the blood flow. In the available literature, we haven't found the cases of missile pulmonary embolism resulting from a mine-blast injury. In the majority of the described cases, the projectile-embolus didn't pass with the bloodstream further than the right ventricle because it was delayed within the tricuspid valve cusps and tendon chords, or the bullet-embolus retrogradely moved against the blood flow [1, 8, 26]. About half of the projectile-emboli fall into the right ventricle, 1/3 — into the pulmonary artery, and the rest — into the hepatic vein, inferior vena cava, popliteal, femoral and common iliac vein [26].

Classification. Depending on the nature of the vessel into which the bullet-embolus falls, the missile embolism is divided into arterial embolism and venous embolism [7, 10, 31]. Overall, approximately 75—80 % of reported cases are arterial, embolizing to the periphery, and 20—25 % of cases are venous [1, 3, 4, 6, 10, 26]. Arterial embolization most often occurs in the lower extremities, more commonly in the left side than in the right side [6].

The review of case reports showed that venous embolism was caused by primary injuries of the following veins:

- external iliac vein [6, 21, 43];
- inferior vena cava [23, 31];
- portal vein [18];
- renal vein [22];
- femoral vein [10];
- right ventricle of the heart [14];
- cranial venous sinus [7, 9, 12, 13, 30];
- subclavian vein [28];
- neck veins [31, 42].

Depending on the pattern of the venous projectile-embolus movement after falling into the blood flow, the next scenarios of bullet-embolus migration can be distinguished:

- antegrade venous embolism — a bullet-embolus migrates with the blood flow towards the right ventricle of the heart; in cases of passage through the tricuspid valve, a missile-embolus gets to the pulmonary artery [7, 10, 23, 43];
- retrograde venous embolism — a bullet-embolus moves against the blood flow under the influence of gravity in the distal direction from the location of the vein injury [3, 35, 25];
- paradoxical embolism — a shrapnel-embolus gets into the bloodstream and reaches the right side of the heart, and then through the arteriovenous fistula or perforation of the atrioventricular septum, or ventricular defect, gets through the patent oval foramen and falls into the arterial bed causing arterial embolism (venous-arterial paradoxical embolism); the cases of the arteriovenous paradoxical embolism have also been described [5, 8, 22, 24, 27, 29, 36, 41];
- «roaming» venous embolism — a projectile-embolus is alternately displaced within the venous bed back and forth: in the direction to the heart (along the blood flow) and then in the direction from the heart (against to the blood flow) [10, 31]; sometimes, a bullet-embolus can migrate into the contralateral eponymous vein on the other side of the injured vein [6].

Retrograde venous embolism is extremely rare, with only 14 cases presented in the literature [3, 6]. Retrograde venous embolization occurs in up to 15 % of patients, and the effect of gravity has been suggested as a cause [31].

Depending on the time of the bullet-embolus migration, the following types of venous embolism can be distinguished:

- acute venous embolism, developing immediately or on the first day after injury during evacuation of an injured person [6, 10, 31, 43];
- tardive venous embolism, developing within months or years after injury (there is a case report of the venous tardive missile embolism that developed 14 years after injury [3, 22].

Clinical presentation. Arterial and paradoxical emboli typically migrate peripherally to the extremity and present early with limb or end-organ ischemia [6, 10, 31]. Bullet embolization into the arterial system is generally symptomatic in 80 % of patients and is usually discovered early [25, 31].

Venous bullet embolization, however, is asymptomatic in approximately 70 % of patients [3, 6, 25]. However, missile pulmonary emboli may present clinically with many of the same vital findings that one would suspect in case of thromboembolic pulmonary embolism, including tachycardia, tachypnea, hypoxemia [23], dyspnea, chest pain, hemoptysis [15, 35, 40]. Symptomatic patients with venous embolization may present late, sometimes within months or years after the initial injury [5, 20, 22, 25, 26, 37].

Complications. Potential sequelae of missile venous emboli include delayed embolization to the heart or pulmonary vasculature, arrhythmia, valvular dysfunction, sepsis [6], vascular occlusion with pulmonary infarction, [7, 39], pulmonary abscess, erosion in the bronchus [8], pulmonary gangrene, erosion through the arterial wall and subsequent hemorrhage [15, 23, 41], endocarditis, venous thrombosis, thrombophlebitis, severe hypoxia [31], and death (6 %) [37, 40]. F. L. Shannon et al. reviewed 102 cases of venous bullet emboli from 1930 to 1987 and reported a 25 % overall complication rate [37].

Diagnostic clues. Due to its relative rarity, the possibility of a missile pulmonary embolism isn't

given much consideration when evaluating trauma CTs for complications, such as viscus perforating injuries or free bleeding into the peritoneal/retroperitoneal spaces. Nevertheless, this possibility should not be ignored [23]. Taking into consideration the existing reports of bullet-embolism cases, it is reasonable to define the following diagnostic clues that help define the risks of projectile embolism:

- the changing shrapnel position as seen in the subsequent X-ray images — «roaming bullet» phenomenon [6, 26, 31];
- the presence of entrance perforation but the absence of exit perforation [7, 40];
- the number of entrance bullet holes is larger than the number of exit bullet holes [10];
- the actual location of the fragment according to the X-ray or CT data doesn't correspond with the position of the bullet wound tract [40].

If the above-mentioned diagnostic signs are observed in patient after gunshot injury, the whole-body CT and angiography are justified for specifying a projectile position and evaluation of the distal circulation [7, 10, 40].

Management. The treatment of bullet embolization depends on the location of the bullet and partly on the presence or absence of symptoms [6]. Due to the developed ischemia, most arterial emboli cause immediate symptoms that require emergency surgical intervention [6—8, 26, 27]. Generally, most authors agree that arterial bullet emboli should be retrieved as soon as they are recognized [31].

Asymptomatic venous bullet embolization has historically provoked debates over the need for its removal, but the management guidelines haven't been clearly established [3, 7, 10, 23]. The treatment planning often depends on whether or not the patient is symptomatic: in a symptomatic patient, embolectomy is often pursued, whereas in an asymptomatic patient, some still advocate embolectomy [38, 40], while others promote more conservative measures, such as supportive care [17, 22, 32]. F. L. Shannon reported that about 25 % of patients would suffer eventual morbidity from venous embolization, and the author recommends a mandatory extraction in the acute setting [37]. Whereas, J. B. Kortbeek reported a series of 32 cases of bullet embolism to the pulmonary artery, 14 of which were managed non-operatively. None of the non-operatively managed patients for whom follow-up data were available suffered an adverse effect from the embolus [17]. As reported by some authors, the right ventricular bullet emboli could be observed if the bullet was less than 5 mm, firmly lodged, with no evidence of arrhythmia or valvular dysfunction [27].

Endovascular treatment. The first report of endovascular retrieval of a bullet, performed by G. O. Hartzler in 1980, describes retrieval of a bullet from the right ventricle using a snare device [6, 11]. This was perfected by S. J. Sclafani in 1991, who recommended the application of the balloon occlusion of the proximal vein to prevent procedure-related central embolization [34]. While the number of reported cases remains small, recent publications report growing use and success of endovascular retrieval [26, 29]. So, endovascular extraction should be the first-line treatment of symptomatic cases of pulmonary bullet emboli when feasible [10]. Some authors recommend pulmonary embolectomy in asymptomatic patients only if the bullet is accessible via an endovascular approach, even in the absence of symptoms, to prevent delayed complications [26].

Both successful and unsuccessful cases of endovascular extraction of projectiles are described in the literature. For example, C. O. Carter described a case of successful endovascular retrieval of a bullet from the left external iliac vein using percutaneous angiographic bullet extraction [6]. Whereas, T. Nolan reported about multiple unsuccessful attempts of endovascular extraction of a bullet-embolus from the retrohepatic inferior vena cava; in 2 weeks, the bullet-embolus accidentally migrated to the common iliac vein, from where it was successfully removed by an endovascular method [31]. We didn't find any reports of successful cases of primary endovascular retrieval of a projectile-embolus from the pulmonary artery due to the technical difficulties of this procedure. Thereby, M. G. Yamanari reported about multiple unsuccessful attempts of bullet retrieval from the lingular segment of the left pulmonary artery [43].

G. G. Fernandez-Ranvier described several attempts of right internal iliac vein laser embolization and inferior vena cava filter placement to prevent a venous missile embolism. However, all these attempts were unsuccessful and a bullet-embolus migrated to the pulmonary artery [10].

Review of 45 cases of venous bullet emboli from 1987 to 2010 revealed 14 of 45 patients (31 %) were managed successfully without extraction [26]; 26 cases (58 %) were managed by surgical intervention. Some authors were in favor of extraction of the missile in all patients with intracardiac missiles and of observation in selected asymptomatic patients with pulmonary arterial emboli [26, 31].

In the presented case, we didn't try to perform endovascular extraction of a projectile from the pulmonary artery because the patient had an associated severe abdomino-orthopedic mine-blast injury with gunshot damage of the hollow body

organs (duodenum and transverse colon) and inferior vena cava. These complex injuries required multiple urgent surgical interventions to manage comorbid damages of the duodenum and transverse colon, as well as complications of these injuries. Furthermore, the patient didn't have any clinical manifestations or complications of pulmonary artery missile embolism. F. L. Shannon advises the same management of the case, even if more than 6 weeks have passed after injury [37].

Open surgery. Surgical intervention should be considered when endovascular procedures fail [10]. A review of 17 patients with bullet emboli in the pulmonary arteries found that seven out of nine patients died when embolectomy wasn't performed, compared to no deaths in eight patients who underwent surgical embolectomy [39].

We consider open surgery an optimal method for surgical treatment of patients with projectile pulmonary artery embolism who were injured more than 2 months ago. The fragment lodges firmly in the vessel wall over time, which is one of the causes of unsuccessful endovascular extraction of a bullet. The video endoscopy is used for a bullet extraction in the clinics with technologically advanced equipment for video-assisted thoracic surgery which is operated by experienced and specially trained surgeons. We didn't consider this type of surgical procedure due to lack of experience in performing such operations.

The substantial risk of surgery, involving the pulmonary artery, and even endovascular intervention within the artery, must be carefully weighed so as to avoid potential long-term embolus-related complications in each particular clinical case [28].

Complex wound. It should be noted that in the majority of cases, shrapnel venous embolism resulted from a single gunshot vascular injury. In the literature, we found only three clinical reports of venous bullet embolism caused by magistral vessel wound associated with a gunshot injury of the internal organs: 2 cases of magistral vein wound associated with a terminal ileum injury [6] and 1 case of a through and through injury to the liver, small intestinal injury at two locations, and a single injury to the infrarenal vena cava [31]. An overview of the previously published clinical reports showed that the cases of associated abdomino-orthopedic wound with an inferior vena cava injury complicated by venous missile embolization of the pulmonary artery were not described in the scientific literature. Lack of the information on this issue makes our study original and novel. The presence of concomitant internal injuries can significantly change the above-described management of patients with projectile venous embolism. It was to some extent outlined based on the analysis of almost 200 cases of missile embolism. First of all, the damage-control tactics and the concept of «golden hour» must be applied to wounded patients, including their evacuation to the hospital stage of surgical care within 60 minutes [16]. Further accumulation of experience in the management of missile embolism in patients with severe associated injuries of the internal organs will allow developing guidelines for the treatment of these patients.

Conclusions

Major vein gunshot wounds can be associated with bullet penetration into a vein lumen and its further migration to the right side of the heart and pulmonary artery. Patients with a missile wound and no exit gunshot perforation should be examined using the whole-body CT for determining possible migration of a projectile with the blood flow. Patients with asymptomatic pulmonary artery embolism should be managed non-operatively as all attempts of endovascular extraction of a bullet are usually unsuccessful. In case of symptomatic pulmonary artery projectile embolism, it is reasonable to consider the possibility of open thoracic surgery.

Declaration of interests

The authors declare that they have no competing interests.

Funding. The study received no funding.

Ethics approval and written informed consents statements

The study was approved by the ethical committee at Bogomolets National Medical University and written informed consent to participate in the study was obtained.

Author contributions

I. Tsema: acquisition of data, analysis and interpretation of data, drafting of manuscript; I. Khomenko: study conception and design, acquisition of data, drafting of manuscript; Y. Susak: study conception, critical revision of manuscript, D. Dubenko: analysis and interpretation of data, drafting of manuscript.

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Поєднане поранення нижньої порожнистої вени з уламковою емболією легеневої артерії: клінічне спостереження та огляд літератури

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Кульова емболія легеневої артерії — це рідкісне та непередбачуване ускладнення вогнепальних та мінно-вибухових поранень. Діагностика кульової емболії залишається значним лікувально-діагностичним викликом як для невідкладних, так і для військових хірургів. У літературі трапляються поодинокі повідомлення про таке ускладнення вогнепальних поранень і немає жодних системних спостережень цієї патології. Незважаючи на те, що кульова емболія є рідкісним клінічним феноменом, його наслідки можуть бути катастрофічними для життя та здоров'я пораненого.

Клінічне спостереження. Чоловік віком 34 років отримав тяжке поєднане скелетно-абдомінальне мінно-вибухове поранення з вогнепальними пораненнями внутрішніх органів (дванадцятипала і поперечна ободова кишка), нижньої порожнистої вени та обох нижніх кінцівок. Масивна заочеревинна кровотеча з нижньої порожнистої вени зупинена крайовим ушиванням судини неперервним швом. Проведено первинну хірургічну обробку поранень дванадцятипалої та товстої кишок з первинним ушиванням ранових дефектів. Множинні багатоуламкові переломи нижніх кінцівок стабілізовані за допомогою апаратів зовнішньої фіксації. З огляду на наявність множинного багатоуламкового вогнепального поранення пацієнтові проведено комп'ютерну томографію всього тіла, за результатами якої в правій середній дольовій гілці легеневої артерії виявлено фіксований уламок-ембол. У ранній післятравматичний період у пораненого не було жодних клінічних виявів кульової емболії легеневої артерії, а тяжкість його стану була зумовлена поєднаною множинної торако-абдомінальною травмою. В післятравматичний період у хворого виникла низка ускладнень: множинні некрози та перфорації поперечної ободової кишки, що спричинили каловий перитоніт, неспроможність швів дванадцятипалої кишки, що призвело до формування зовнішньої дуоденальної нориці, множинні рани м'яких тканин нижніх кінцівок ускладнилися рановою інфекцією. Зазначені ускладнення потребували проведення етапних хірургічних втручань. Після стабілізації стану хворого спроб ендоваскулярної ретракції уламка-ембола з легеневої артерії не здійснювали через наявність тяжких поєднаних скелетно-абдомінальних поранень, їх ускладнення та безсимптомний перебіг кульової емболії легеневої артерії. Успішне видалення уламка-ембола проведено на 80-ту добу після поранення: виконано торакотомію, видалення уламка із середньої дольової артерії, накладено судинний шов, через відсутність явищ склерозу чи інфаркту легені резекції легеневої паренхіми не проводили. Пацієнта у задовільному стані виписано зі стаціонару на 168-му добу після мінно-вибухового поранення для амбулаторної психосоматичної реабілітації.

Висновки. Пацієнтам зі сліпими множинними уламковими проникаючими вогнепальними пораненнями показано проведення комп'ютерної томографії всього тіла для виявлення потенційної внутрішньосудинної міграції уламків з током крові. У пацієнтів із безсимптомною кульовою емболією видалення уламка-ембола може бути відстрочене до завершення хірургічного лікування провідного поранення та його ускладнень. При розвитку клінічних виявів кульової емболії легеневої артерії доцільно розглянути можливість виконання відкритої торакальної операції.

Ключові слова: уламкове поранення, нижня порожниста вена, легенева артерія, венозний кульовий емболізм.

FOR CITATION

Tsema I, Khomenko I, Susak Y, Dubenko D. Associated projectile inferior vena cava wound with subsequent pulmonary artery missile embolization: a case report and literature review. General Surgery (Ukraine). 2021:1;48-59. http://doi.org/10.30978/GS-2021-1-48.

UDC 616.33-089.843-06(048.8)
DOI http://doi.org/10.30978/GS-2021-1-60

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Early and late complications after gastric bypass: A literature review

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Over the last few decades, excess weight and obesity have become a considerable health problem that has a lasting impact on communities worldwide. According to the WHO, about 1.9 billion people over the age of 18 are overweight [32]. Obesity accounted for about 4.7 million premature deaths in 2017. Globally, obesity was associated with an increase in mortality rate from 4.5 % in 1990 to 8 % in 2017 [32]. Bariatric surgery is currently recognized as the most effective treatment option for morbid obesity. Over the past 10 years, gastric bypass surgery has proved more effective than any other surgical methods due to its optimal metabolic effects.

The aim of the review is to carry out an analysis of literature data in order to identify main complications after gastric bypass in patients with obesity.

The complication rate after bariatric surgery decreased from 10.5 % in 1993 to 7.6 % in 2006 [3]. The mortality rate after bariatric surgery was 0.08 % within 30 days after surgery and 0.31 % after 30 days [13]. According to the BOLD study (2010), for 57,918 bariatric operations, the complication rate was 6,240 (10.77 %) and the mortality rate was 78 (0.135 %), within 30 days after surgery — 0.089 %, within 90 days after surgery — 0.112 %. Roux-en-Y Gastric Bypass (RYGB) was carried out in 30,864 cases, and 4,588 (14.87 %) patients developed postoperative complications. Early complications include anastomotic leaks (0—5,6 % for laparoscopic approach and 1,6—2,6 % — for laparotomy), small bowel obstruction caused by a blood clot (0—0,5 %), bleeding from the sutures (1,5 %), and thromboembolic complications (0,2—5 %). Late complications include stenosis of the gastrointestinal tract (3—27 %), marginal ulceration (MU) — 0,6—16 %, an incarcerated Petersen's space hernia — 2,51 %, perforation of the stomach and small intestine (1—2 %), gastrogastric fistula formation — 1,5—6,0 %, weight regain (to 17,1 %).

Increasing global demand for bariatric surgery as the best option for the management of excess weight and obesity necessitates more detailed investigation of possible complications it may induce. Therefore, further research is required to develop and study new effective methods for prevention and treatment of complications after surgical treatment of patients with morbid obesity.

Keywords
obesity, bariatric surgery, gastric bypass, anastomotic leaks, small bowel obstruction, marginal ulceration, Petersen's space hernia, gastrogastric fistula, weight regain.

ARTICLE • Received 2021-11-01 • Received in revised form 2021-11-18

Over the last few decades, excess weight and obesity have become a considerable health problem that has a lasting impact on communities worldwide. According to the WHO, about 1.9 billion people over the age of 18 are overweight [32]. Obesity accounted for about 4.7 million premature deaths in 2017. Globally, obesity was associated with an increase in mortality rate from 4.5 % in 1990 to 8 % in 2017 [32]. Bariatric surgery is currently recognized as the most effective treatment option for morbid obesity. Over the past 10 years, gastric bypass (GBP) surgery has proved more effective than any other surgical methods due to its optimal metabolic effects. According to the latest global statistics, presented in the statistical report «Fifth IFSO Global Registry Report 2019», which included data from 61 countries, 833,687 bariatric operations were performed between 2014 and 2018. However, a respective structural analysis was carried out for the period 2015—2018. It showed that 520,983 bariatric operations were performed within this time frame, including 305,242 (58.6 %) operations done as a sleeve gastrectomy, 162,613 (31.2 %) gastric bypass surgeries, 21,613 (4.1 %) mini-gastric bypass surgeries, 19,255 (3.7 %) gastric banding procedures and 8,665 (1.7 %) other surgical interventions. The vast

majority of operations (99.1 %) were conducted using laparoscopic abdominal access technique [13].

The complication rate after bariatric surgery decreased from 10.5 % in 1993 to 7.6 % in 2006 [3]. The mortality rate after bariatric surgery was 0.08 % within 30 days after surgery and 0.31 % after 30 days [13]. According to the BOLD study (2010), for 57,918 bariatric operations, the complication rate was 6,240 (10.77 %) and the mortality rate was 78 (0.135 %), within 30 days after surgery — 0.089 %, within 90 days after surgery — 0.112 %. Roux-en-Y Gastric Bypass (RYGB) was carried out in 30,864 cases, and 4,588 (14.87 %) patients developed postoperative complications [24].

Early complications include anastomotic leaks, small bowel obstruction caused by a blood clot, bleeding from the sutures, and thromboembolic complications [9].

Late complications include stenosis of the gastrointestinal tract, gallstone disease, marginal ulceration (MU), an incarcerated Petersen's space hernia, intussusception, perforation of the stomach and small intestine, gastrogastric fistula (GGF) formation, weight regain, lack of vitamins and microelements [6].

According to various statistical data, anastomotic leakage (AL) after gastric bypass surgery is 0—5.6 % for laparoscopic GBP and 1.6—2.6 % for open GBP. In specialized bariatric centers, this variable reaches 1.5 % [1, 6, 19, 23, 32].

According to the day of appearance, AL can be divided into early (within 4 days after surgery), medium-term (between day 5 to 9 after surgery), late (after 10 or more days) [19, 24, 52]. According to the severity, AL can be graded as type I, which is manifested by a small defect with or without minor systemic disorders, and type II, which is diagnosed when large defects with systemic manifestations or air-fluid accumulation in the abdominal cavity are observed. Anastomotic leaks can be localized around the sites of the gastrojejunal anastomosis (53.3 %), staple lines on the gastric pouch (18.3 %), staple lines in the place of the jejunal transection (15.0 %), the jejunojejunal anastomosis (5.5 %) and staple lines on the excluded gastric remnant (1.7 %) [19]. The development of AL is influenced by mechanical and ischemic factors that interfere with the normal healing process. However, another complicating factor is associated with an increase in pressure within the stomach and small intestine, which results in greater tension along the suture [42, 67]. Other factors that may contribute to the development of this complication are advanced age over 50 years, male gender, BMI > 50 kg/m^2 and previous bariatric surgery [28]. Anastomotic leaks that appear in the first 5 days after surgery are most often linked to the application of improper operation technique, and those that develop after 5 days are most likely the result of local ischemia or infection [5]. To prevent the occurrence of AL, various techniques are currently used for suture reinforcement with fibrin sealant [9]. An important factor that reduces the incidence of AL is the experience of the surgeon. The study of L. El-Kadre et al. (2013) that included 2,281 patients, who underwent laparoscopic RYGB, revealed that after 500 surgical procedures, the operation time and postoperative complication rates reduced. The mortality rate was 0.43 %, the main cause of death was pulmonary embolism and AL (0.14 % each) [26].

Surgery is the gold standard of AL treatment. Surgical treatment includes restoration of the gastrointestinal tract integrity, drainage of the abdominal cavity and prevention of future complications [32]. Endoscopic interventions are used in both the diagnosis and treatment of AL. The endoscopic therapy includes stent placement at the defect site, defect clipping, AL site drainage, Vacuum-Assisted Closure therapy, and fibrin sealant injections [66]. During endoscopic interventions, the technique of vacuum-associated endoscopic drainage is also used. A nasogastric tube with a sponge at the distal end, which is fixed with sutures, is inserted. An endoscopic device is guided into the lumen of the organ to place the sponge in it. Then a negative pressure is created in the area of the defect through the nasogastric tube to allow the sponge to absorb fluid and remnants of the non-viable tissue. The pressure ranges from –125 to –75 mm Hg. The sponge should be changed every 3—4 days [37, 8]. The level of full resolution is from 85 % to 100 % [37].

Acute mechanical bowel obstruction (BO) caused by a blood clot is very rare (up to 0.5 %) after laparoscopic RYGB. The most common localization of BO is the site of the jejunojejunal anastomosis. Most obstructions occur 2—5 days after surgery. Computed tomography of the abdominal cavity is the main method of diagnosing bowel obstruction, including BO arising from a blood clot [35]. On radiography of the organs of the abdominal cavity, there are signs of intestinal obstruction, and the contrast study of the gastrointestinal tract allows detecting the distention of the stomach and jejunal loops [60]. In the cases described in the meta-analysis, patients underwent relaparotomy with enterotomy and removal of a blood clot from the lumen [53].

Postoperative bleeding after GBP occurs in 1.5 % of patients and is associated with high mortality, increased hospital stays, and other complications [76]. Bleeding events are observed around the sites of the gastric pouch (30 %), the excluded

gastric remnant (40 %), and the jejunojejunal anastomosis (30 %) [36]. Postoperative bleeding events after GBP are identified as early and late (up to 30 days and after 30 days from the time of surgery). From all bleeding events after RYGB, early bleeding accounts for 71.4 % of all cases and usually appears after 3.2 days. 43 % of bleeding events occur within 24 hours after surgery [36].

About 80 % of acute postoperative bleeds in patients after bariatric surgery stop on their own and don't require any medical attention [32]. Immediate administration of proton pump inhibitors is indicated for patients with bleeding into the stomach or intestine [6]. The patients with severe bleeding require urgent surgical intervention. Endoscopic, laparoscopic or open access techniques are used. If the source of bleeding is in the organ cavity and is accessible for endoscopic treatment, clipping or epinephrine injection is performed. The use of electrosurgery is not recommended due to the high risk of perforation in the late period [29]. Indications for surgery are impaired hemodynamics of the patient, bleeding into the abdominal cavity, the bleeding site is inaccessible for endoscopic treatment, or the endoscopist doesn't have appropriate skills and training in endoscopic hemostasis techniques.

Both laparotomy and laparoscopy are used. The main mission of the surgeon is to find the source of bleeding, evacuate hematoma and perform hemostasis [29]. Angioembolization of the left gastric artery has been used in isolated studies to stop bleeding, but due to the high risk of the gastric pouch ischemia, it is recommended only in case of ineffective endoscopic treatment in patients with severe course and contraindications for reoperation [30].

Internal herniation (IH) after RYGB occurs in about 2.51 % of patients. Symptoms most often appear between 16—35 months [31]. According to the location, hernias are most frequently detected in the mesentery of the colon (69.0 %), Peterson's space (18.0 %), and at the site of the jejunojejunal anastomosis (14.4 %). The mortality rate is 1.17 %. The major risk factor for internal herniation is rapid weight loss [32]. The studies indicate a reduction in IH if the mesenteric defects are closed. The mesenteric defects are described as the places of the main localization of IH. They include a defect in the mesentery of the colon, which is formed during surgery and through which the alimentary loop passes, Peterson's space, which occurs between the mesentery of the alimentary and biliopancreatic loops after the jejunal loop transection and mobilization, as well as jejunal defect, which can develop at the site of the side-to-side jejunojejunal anastomosis which is constructed by suturing the efferent loop to the afferent loop with interrupted sutures [9]. N. Geubbels et al. (2015) state that the best option is the antecolic procedure with closure of all defects (Petersen's space, jejunal defect) that reduces the incidence of IH (1.0 %) [33]. Clinically, the most common manifestation was abdominal pain after meal and it was noted in 24 (53.4 %) patients. Abdominal pain syndrome with nausea was seen in 8 (17.8 %) patients. Abdominal pain syndrome with nausea and vomiting was observed in 8 (17.8 %) patients. Acute abdominal pain was present in 2 (4.4 %) patients. Acute abdomen was noted in 1 (2.2 %) patient [38]. Amylase/lipase levels were higher in patients with acute obstruction than in patients with chronic symptoms (64 % vs. 28 %). Patients with biliopancreatic loop obstruction also had more elevated levels of amylase/lipase than patients without obstruction (65 % vs. 21 %). The most elevated levels were observed in acute obstruction of the biliopancreatic loop (94 %) compared with acute alimentary obstruction (27 %). It is evidence of the existing link between increased amylase/lipase levels and acute obstruction of the biliopancreatic loop [70]. Instrumental examinations include abdominal radiography and computed tomography of the abdominal cavity. M. S. Altieri et al. (2015) developed an algorithm for diagnosing IH in patients after RYGB. The study included 52 patients with IH. The findings of the study showed that the sensitivity of CT for the diagnosis of IH was 76 %, specificity was 60 %. However, when the blood neutrophil levels were included into the evaluation process, the sensitivity increased to 96 % [48].

The onset of symptoms of intestinal obstruction due to IH requires immediate surgical treatment. Laparoscopic access is used at an early stage, when there is no significant distention of the intestinal loops. Laparotomy is recommended in case of severe peritonitis. Typical IH sites should be checked. If a hernia is found, it is fixed, and the defect is closed with a continuous or non-absorbable purse-string suture. When strangulation occurs, resection of the unviable part of the intestine is performed with the formation of anastomosis [16, 57].

Gastro-gastric fistulas occur in 1.5—6.0 %. The causes of fistulas are insufficient transection of the stomach, tissue ischemia, leakage of intestinal contents into the excluded gastric remnant, the presence of foreign objects (catgut and staples, improper suturing) [40]. Gastro-gastric fistulas usually form 25 days after a diagnosed gastrojejunal anastomotic failure. Gastro-gastric fistulas are classified as type 1 that are located at a distance of 2 cm from the gastrojejunal anastomosis, and type 2 that are located at a distance of less than 2 cm from the

gastrojejunal anastomosis [10, 62]. L. Carrodeguas et al. (2005) identified 6 main causes of Gastro-gastric fistulas, including iatrogenic (incomplete gastric transection, presence of perigastric fat included in the transected tissue), gastrojejunal anastomotic leaks, technical reasons, gastric wall tissue migration after surgery, ulceration and perforation, foreign body erosion resulting from the placement of preanastomotic rings to prevent dilatation of the anastomosis [10].

The tactics of treatment of patients with GGFs include observation, conservative treatment, surgery or endoscopic intervention. Observations are recommended for patients with Gastro-gastric fistulas, which are accidentally found and do not cause any discomfort [9]. Indications for surgical treatment are ineffectiveness of conservative treatment, worsening of symptoms that reduces the quality of life of patients, weight gain or insufficient weight loss, gastrointestinal bleeding associated with ulcers, large Gastro-gastric fistulas [9]. The tactics depend on the postoperative period, the cause, the presence of the ulcer, and the patient's general condition. The type 1 Gastro-gastric fistulas require transection of the fistula tract that is carried out vertically to the gastrojejunal anastomosis. The type 2 Gastro-gastric fistulas necessitate full resection of the fistula tract and the gastrojejunal anastomosis which is followed by the formation of a new anastomosis [62]. Laparoscopic access is more optimal than laparotomy if the operation is initially performed laparoscopically, and Gastro-gastric fistulas are diagnosed at an early stage, as late diagnosis reveals the distorted anatomy due to inflammation and adhesions [18, 30]. Large Gastro-gastric fistulas require surgical removal of the excluded gastric remnant together with the fistula tract [18, 64]. Endoscopic obturation of the fistula tract opening is performed by using fibrin sealant, suturing of the opening, and clipping [9, 29, 55].

Marginal ulceration is a defect of the mucous membrane that penetrates through its muscular layer around the sites of the alimentary loop, the gastric pouch or excluded gastric remnant. They occur in 0.6—16.0 % [58, 15]. of patients after laparoscopic RYGB, a certain number of patients with asymptomatic ulcers should also be taken into account. In a study by A. Csendes et al. (2009), 315 patients underwent Esophagogastroduodenoscopy 1 month and 17 months after laparoscopic RYGB. Marginal ulceration was diagnosed in 25 patients (6.0 %) after 1 month, 7 of whom were asymptomatic. After 17 months, only 1 new ulcer and 1 recurrent ulcer were diagnosed after Proton-pump inhbitor therapy [20]. From 9 % to 33 % of patients with MU require surgical treatment [58, 20, 11]. Marginal ulcers complicated by perforation are found in about 1—2 % of patients after RYGB, whereas 20 % of MU turn out to be complicated by perforation [15]. They most commonly occur between 3 and 24 months after surgery. About 20 % of perforations occur in patients with asymptomatic MU, and risk factors are nonsteroidal anti-inflammatory drug, smoking, and glucocorticosteroids [27]. The treatment is surgical, open or laparoscopic, with drainage of the abdominal cavity and suturing of the defect. In the group operated laparoscopically, 1 patient developed hydrothorax, which required drainage under ultrasound control. In the group of laparotomies, 1 patient developed pulmonary embolism, and 1 patient died of sepsis and multiple organ failure [39].

About 5 % of ulcers that form after laparoscopic RYGB are complicated by bleeding, with acute massive bleeding developing in 1.1—4.0 % [25, 54]. Administration of anticoagulants or antiplatelets increases the risk. Conservative tactics include intravenous access, infusion therapy, and transfusion if needed. Insertion of a nasogastric tube is avoided. Urgent EGD is recommended if the patient has stable hemodynamics, with clipping or epinephrine injection. The rate of re-bleeding after EGD is 22 % and 4 % of them require surgery [73].

Stenosis after gastric bypass procedure usually occurs in 3—27 % of patients 3—4 weeks after surgery [14, 21, 69, 34, 43]. After laparoscopic RYGB, strictures and stenoses are most frequently found at the site of the gastrojejunal anastomosis. Risk factors for the anastomotic stricture after laparoscopic RYGB are advanced age over 60 years, circular staple suture, postoperative anastomotic failure and ulcer formation. In a meta-analysis of H. Khalayleh et al. (2018), there is evidence of more frequent development of the anastomotic stricture after using a circulatory stapler [41].

The treatment includes endoscopic balloon dilatation of the stricture. It is recommended to use a balloon with a diameter of up to 18 mm during the first dilatation. The use of balloons of larger diameter can cause rapid emptying of the gastric pouch and lack of effect from the operation [46, 69]. The longer the postoperative period ($p = 0.007$) and the smaller the diameter are after the first dilatation ($p = 0.015$), the lower dilatation efficiency is achieved. Perforations occurred in 3 patients (1.8 %) after conservative treatment [21]. According to a cohort study of 36,362 patients after RYGB, registered in the Scandinavian Registry of Bariatric Surgery, the gastrojejunal anastomotic stricture occurred in 101 patients within 1 year after surgery. Risk factors were defined as advanced age over 60 years OR — 6.2 (95 % CI 2.7—14.3), use of a circular stapler for the formation

of the gastrojejunal anastomosis OR — 2.7 (95 % CI 1.4—5.5), postoperative insufficiency of the anastomosis OR — 8.9 (95 % CI 4.7—17.0), the presence of marginal ulcers OR — 30.0 (95 % CI 19.2—47.0). 75 % of strictures were diagnosed within the first 70 days after surgery. Two or fewer endoscopic dilatations were 50.0 % effective. Perforations occurred in 10.0 % of patients during dilatation. In general, the risk of perforation during endoscopic dilatation is 3.8 % [4]. 38.0 % of patients require more than 1 endoscopic dilatation. The complication rate after dilatation is 4.0 %. In the case of refractory stricture, steroid injections are used before dilatations. In case of perforations, it is recommended to carry out conservative treatment, and stents are used for large perforations [7]. For chronic refractory strictures found before dilatations, stents have been used in isolated studies. The authors recommend the placement of stents only in patients with severe strictures as part of preparation for surgical treatment [61, 12, 74].

After bariatric intervention during the first 18—24 months, patients have the «honeymoon» period, when they experience weight loss. Most patients subsequently stop losing weight and gradually gain weight. According to various studies, weight gain occurs 2—5 years after surgery [45, 49, 17].

Some researchers consider weight gain as the difference between the highest and lowest body weight after surgery; increase in Body Mass Index; % EWL = lost body weight (kg) : overweight (kg) · 100, or the difference between the weight before and after the operation expressed as a percentage [5, 75, 47]. Weight gain occurs in about 20 % of patients after laparoscopic RYGB [65, 22, 51]. In the study, weight gain of more than 10 % of the lowest body weight in the postoperative period was recorded in 24 % of patients [75]. In a 2007 study, from 782 patients, weight gain was noted in 46 % two years after surgery and in 64 % 4 years after surgery [49]. Comparing weight 1 and 2 years after surgery, a 5 % increase was identified in 33 % of patients [71]. The review of 16 scientific studies allowed classifying of the causes of weight gain into 5 groups: eating disorders, psychological problems, endocrine or metabolic disorders, physical inactivity and anatomical surgical factors [63].

Due to the negative psychological and physical impact of weight regain, revisional bariatric surgeries are recommended 1 year after surgery, but it should be borne in mind that the risk of postoperative complications for secondary bariatric surgeries is higher than for the primary procedures [63]. The review of 24 studies showed that 866 patients had significant weight loss in the early period after revisional bariatric surgery, which followed unsuccessful RYGB. Secondary bariatric surgery was performed with the application of 5 different techniques, but only 3 of them, including biliopancreatic shunting, distal gastric bypass and gastric banding, led to weight loss with a low incidence of complications. Endoluminal interventions and creation of a new Roux loop are not recommended [72]. Endoscopic techniques that are widely used nowadays include Apollo OverStitch (Apollo Endosurgery, Austin, Texas), which is the formation of a fold and reduction of the gastrojejunal anastomosis diameter, and sclerotherapy and OTSC (Over-The-Scope-Clip) clipping, in which special clips are used to reduce the gastrojejunal anastomosis diameter [44]. Sclerotherapy is performed by injecting a sclerosant, usually Morrhuate Sodium, into the tissue at the site of the gastrointestinal anastomosis to increase the restrictive effect. The study shows that 91.6 % of patients lose weight 1 year after injection [44].

Thus, increasing global demand for bariatric surgery as the best option for the management of excess weight and obesity necessitates more detailed investigation of possible complications it may induce. Therefore, further research is required to develop and study new effective methods for prevention and treatment of complications after surgical treatment of patients with morbid obesity.

Declaration of interests

The author declare no conflicts of interest.

Funding. The work is a fragment of the planned research work of the Department of General Surgery No2 of Bohomolets National Medical University «Implementation of minimally invasive surgical techniques in the treatment of pathologies of the abdominal cavity, anterior abdominal wall, morbid obesity by fast-track technique» (State registration number 0118U000147).

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Ранні та пізні ускладнення після шунтування шлунка. Огляд літератури

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Ожиріння та надмірна маса тіла вже протягом багатьох років є важливою суспільною проблемою. За даними ВООЗ, близько 1,9 мільярда людей старше 18 років мають надмірну масу тіла. Близько 4,7 мільйонів людей в 2017 році померли передчасно внаслідок ожиріння. Глобально смертність від ожиріння зросла з 4,5 % в 1990 році до 8 % в 2017 році. Баріатрична хірургія на сьогодні визнана найбільш ефективним методом лікування морбідного ожиріння. Серед баріатричних оперативних втручань за останніх 10 років, шлункове шунтування підтвердило свою ефективність через оптимальний метаболічний ефект.

Мета огляду — провести аналіз даних літератури для визначення основних ускладнень після шлункового шунтування у хворих з ожирінням.

За даними оглядку літератури, кількість ускладнень після баріатричних операцій зменшилась з 10,5 % в 1993 до 7,6 % в 2006. Рівень смертності після баріатричних втручань становить 0,08 % в перші 30 днів після операції, і 0,31 % після 30 днів. За результатами дослідження BOLD (2010) серед 57 918 баріатричних втручань рівень ускладнень становив 6240 (10,77 %), а рівень летальності — 78 (0,135 %), протягом 30 днів після втручання — 0,089 %, протягом 90 днів — 0,112 %. Для гастрошунтування за Ру (30 864 втручання) рівень ускладнень був 4588 (14,87 %). До ранніх ускладнень належать — неспроможність анастомозу (0—5,6 % для лапароскопічного доступу, та 1,6—2,6 % для лапаротомічного), обтураційна кишкова непрохідність кров'яним згустком (0—0,5 %), кровотеча з ділянки швів (1,5 %), тромбемболічні ускладнення (0,2—5 %). До пізніх ускладнень — стеноз ділянки шлунково-кишкового тракту (3—27 %), маргінальна виразка — 0,6—16 %, защемлена внутрішня грижа (грижа Петерсена) — 2,51 %, перфорація стінки шлунка та тонкої кишки (1—2 %), шлунково-шлункова нориця — 1,5—6,0 %, рецидив морбідного ожиріння (до 17,1 %).

Таким чином, враховуючи світову тенденцію збільшення кількості баріатричних операцій, на часі — вирішення питання можливих їх ускладнень. Через це, необхідним є пошук нових ефективних методів профілактики та лікування ускладнень після хірургічного лікування пацієнтів з ожирінням.

Ключові слова: ожиріння, баріатричні операції, шлункове шунтування, неспроможність анастомозу, обтураційна кишкова непрохідність, маргінальна виразка, грижа Петерсена, шлунково-шлункова нориця, рецидив ожиріння.

FOR CITATION

Nevmerzhytskyi VO. Early and late complications after gastric bypass: A literature review. General Surgery (Ukraine). 2021:1;60-66. http://doi.org/10.30978/GS-2021-1-60.

UDC 616.34-008.14/.15-02-092
DOI http://doi.org/10.30978/GS-2021-1-67

ISSN 2786-5584 (Print)
ISSN 2786-5592 (Online)

Chronic constipation: modern view on the problem. A review

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Chronic constipation is a frequently diagnosed heterogeneous pathology that significantly impairs the quality of life in all population groups and its frequency increases with age. It commonly affects up to 10—15 % of the population. There are numerous classifications of constipation due to a great number of disorders that cause it. The types of constipation are identified based on the etiology or mechanism of its development. Different criteria are used to specify the categorization of constipation, but it is still difficult to find one general classification including all types of constipation. The Rome IV criteria categorize disorders of chronic constipation into four subgroups. The treatment depends on the subtype. The significant increase of constipation cases is observed nowadays. This disorder is facilitated by a sedentary lifestyle, insufficient amount of fiber and fluid in the diet, a wide range of diseases that directly lead to the development of chronic constipation, congenital and acquired pathologies, abnormal intake of laxatives and opioids or a combination of these factors. Despite numerous publications on slow transit constipation, the latter is still the subject of research for many specialists. A lot of recent scientific works have been dedicated to the immunohistochemical studies of interstitial pacemaker cells. The numbers of markers they express were found. Consequently, the investigations of modern scientists are aimed to develop and implement new laboratory methods for determining the indications for surgical treatment depending on a diagnosed disorder of the intestinal neurophysiology. These methods will ensure a differentiated selection of patients for surgical treatment. The step approach to the diagnosis of chronic constipation allows choosing an adequate treatment method in order to improve symptoms, the quality of life, and patient satisfaction. The literature review indicates that surgery still remains the most radical treatment method for patients with slow transit constipation.

Keywords
slow transit constipation, laxatives, total colectomy, ileorectal anastomosis.

ARTICLE • Received 2021-11-15 • Received in revised form 2021-11-23

Particular attention to constipation syndrome has been paid since the middle of the 19th century. The first articles on this problem appeared in the scientific medical periodicals. Most of them were descriptive and included the clinical cases from the medical practice and the results of autopsies. Much attention was paid to the clinical picture and such treatment methods as cleansing enemas and various herbal medicines.

At the beginning of the 20th century, Sir William Arbuthnot Lane, a famous Scottish physician and scientist, firstly described refractory chronic disease in women and paid attention to its clinical picture, proposed to treat them surgically. In tribute to the scientist, this type of constipation is called «Lane's disease» [11]. In 1905, the possible causes of constipation syndrome were analyzed, and the characteristic clinical symptoms were described [49].

Thus, the history of chronic constipation treatment began in the depths of centuries. The scientists correctly identified the main links in the development of the disease, and gave them accurate descriptions. In those scientific works, previously unknown mechanisms of constipation were revealed, and new

classifications were introduced. However, to this day, many scientific discoveries on pathogenesis and treatment of chronic constipation are still made.

Chronic constipation commonly affects up to 10—15 % of the population and impairs the quality of life. There are numerous classifications of constipation due to a great number of disorders that cause it. The types of constipation are identified based on the etiology or mechanism of its development. Different criteria are used to specify the categorization of constipation, but it is still difficult to find one general classification including all types of constipation. The Rome IV criteria categorize disorders of chronic constipation into four subgroups: (a) functional constipation, (b) irritable bowel syndrome with constipation, (c) opioid-induced constipation, and (d) functional defecation disorders, including inadequate defecation propulsion and dyssynergic defecation. The first-line management for these disorders is focused on diet, lifestyle and the use of standard over-the-counter laxatives. The treatment is provided according to the subtype [6].

Constipation is defined as difficulties in defecation: infrequent bowel movements, hard or lumpy stools, excessive straining, and sensation of incomplete evacuation or blockage and, in some instances, the use of manual maneuvers to facilitate evacuation. Acute symptoms typically last up to one week and are commonly precipitated by a change in diet and/or lifestyle (low fiber intake, decreased physical activity, stress, etc.). Chronic constipation is commonly defined by symptoms that persist up to 3 months [48].

Epidemiology

The prevalence of chronic constipation ranges from 3 % to 27 % [76].

The global prevalence of chronic constipation has been estimated as 14 % based on a large metanalysis of 45 surveys, comprising 261,040 adults [80]. In healthy people constipation occurs occasionally as a result of diet, traveling or emotional factors. Females, aged patients and low socioeconomic status patients are affected by chronic constipation more commonly [14, 80]. The population-based survey, using the Rome IV diagnostic questionnaire, revealed the following data: the prevalence of chronic constipation is approximately 9 %, with ~ 6 % of functional constipation (FC) and the remaining 3 % split evenly between irritable bowel syndrome with constipation (IBS-C) and opioid-induced constipation (OIC) [61]. A global epidemiological study of functional gastrointestinal disorders is currently underway. Functional defecation disorders, such as inadequate defecatory propulsion and dyssynergic defecation, always require special diagnostic methods [48, 72]

Constipation may be a symptom of different etiologies, and for this reason, many diagnostic approaches and treatment options are available, ranging from simple lifestyle changes and general measures to sophisticated pharmacological treatments and surgical intrusions. [56, 58, 74] The prevalence of chronic constipation increases with age [19, 82] and consequently is expected to rise over the next few years [81]. European Society of Neurogastroenterology and Motility (ESNM) decided to develop European guidelines to improve the quality of life in patients suffering from common functional and motor disorders. The ESNM guidelines for chronic constipation were also discussed.

Predominance of females in the prevalence of constipation was mostly reported by different authors [62]. According to the studies, the mean female/male ratio was 1.78 (median 1.58), but differed according to the definition of constipation (1.7 for Rome I, 1.8 for Rome II, and 2.3 for self-reporting of constipation). The epidemiological study in patients with functional constipation based on Rome III Criteria also showed a higher prevalence in female students (17.4 %) than in male students (12.5 %) [52].

Hormonal factors play a significant role in constipated women: luteal phase of the menstrual cycle and the effect of progesterone in pregnant women, pelvic floor muscles damage during childbirth or gynecological surgery. Premenopausal and older women were also compared in order to measure a colon transit time. Premenopausal women aged 25—49 years were shown to have a longer transit time than older women (64.0 vs 59.5 hours; difference 4.6 hours, 95 % CI 1.1—8.1 hours) [32, 67]. The latter means less pronounced gender differences in constipation prevalence in the older population.

Genetic factors may also play a role in FC [16]. Patients with a positive family history of FC showed younger age at onset (median 11—20 years vs 21—30 years, $p < .001$) and longer duration of constipation (20 ± 14 vs 15 ± 13; $p = 0.016$). Much more complications, such as symptomatic hemorrhoids, anal fissure and rectal prolapse (54.2 % vs 40.4 %, $p = 0.034$), fewer precipitating factors leading to the onset of constipation (35.6 % vs 49.1 %, $p = 0.037$), and more frequent use of digital evacuation (27.1 % vs 13.2 %, $p = 0.008$), were observed in patients with a positive family history of FC. W. Ostwani et al. [60] showed significantly higher rates of constipation in parents of children with functional, habitual constipation than in controls (30 % vs 7 % and 42 % vs 9 %, respectively; $p = 0.001$). Thus, individuals of lower social, economic, and educational

levels have a tendency toward higher constipation rates [13]. Additionally, according to another scientific study [53], constipation correlated with a low maternal educational level (1.60; 1.08—2.35). All of the abovementioned can be related to less consumption of fiber, fruit, and vegetables in low socioeconomic status groups [1].

Pathophysiology

Different pathophysiological mechanisms may lead to FC. Constipation can be classified into three categories: functional defecatory disorders, normal colonic transit, and slow colonic transit (STC) [76].

The pathophysiology of constipation, in particular STC, is not completely studied even nowadays. To understand the causes of defecation disorders, it is necessary to know its mechanism. The normal act of defecation requires a series of synchronized actions, including relaxation of puborectalis muscles, pelvic floor lowering with anorectal angle straightening, inhibition of segmental intestinal peristalsis, contraction of anterior abdominal wall muscles and, finally, relaxation of the external anal sphincter with further expulsion of fecal masses. Colorectal motility disorders presenting with constipation include slow-transit constipation (STC, colonic inertia), pelvic floor dysfunction and combination syndromes. Although sometimes it is impossible to draw a clear distinction between these factors [66].

STC typically affects young women, with the onset of symptoms before 25 in most cases. Etiopathogenesis of STC is not clear. Pelvic floor dyssynergia (anismus) is described as inappropriate contraction or failure to relax the pelvic floor during the attempt to defecate. T. Wedel et al. [88] reported that the colonic motor dysfunction in STC is associated with quantitative alterations of the enteric nervous system (oligoneuronal hypoganglionosis), which cannot be detected just by submucosal biopsy because they primarily affect myenteric plexus and external submucous plexus.

The pathogenesis of the slow-transit type of motor-evacuation disorders can be represented by the suppression of the intestinal motor activity which, in turn, slows down the transit of the contents. As a result, we observe an increase in the contact time of the intestinal contents with the mucous membrane, in the reabsorption of fluid with preserved epithelial transport, as well as in the bacterial fermentation of unabsorbed carbohydrates. A change in viscosity and a decrease in the volume of intestinal contents weaken the sensory sensitivity of the intestinal wall to tension, and inhibit its transit, thus slowing down the vicious circle.

The prolonged time of the presence of feces in the intestine leads to its thickening and decreased size, resulting in insufficient pressure on the rectum necessary for defecation reflex. Accordingly, this group of patients requires more pressure for defecation than healthy people. Various physiological and histobiochemical studies have been carried out in order to explain the phenomenon of slow-transit constipation: a decrease in cholinergic and an increase in adrenergic responses [85]; weak gastrointestinal reflex [36]; dyssynergy of rectosigmoid intestinal activity [7]; neurodegeneration [38] of the intestinal wall in the myenteric plexus ganglia and interstitial cells of Cajal (ICC; Latin interstitium — interval) [89]; abnormalities of intestinal neurotransmitters, such as substance P of vasoactive intestinal peptides [45, 77], nitric acid [45, 84]. With regard to the neuropathological aspects of chronic constipation, the intestinal nervous apparatus plays the main role. Cajal cells are very important in impaired intestinal motility in chronic slow-transit constipation. The role of ICC was analyzed in STC patients, with a focus on motility. They found a significantly decreased volume of ICC in all layers of sigmoid colonic specimens in STC patients compared to controls. Neuronal structures within the colonic circular smooth muscle layer were also decreased. Interstitial cells of Cajal are cells that play an important role in the control of spontaneous motility of the gastrointestinal tract (GIT) and serve as pacemakers that set the frequency for slow waves of electrical potential for smooth muscle, which determine the frequency of peristalsis in various parts of the gastrointestinal tract [39].

Interstitial cells of Cajal are derivatives of the mesenchyme, localized in the interstitium between nerve endings and smooth muscle cells. Electrophysiological evidence of these cells in establishing the slow waves rhythm of smooth muscles was obtained at the end of the 20th century. Interstitial cells of Cajal are found in all parts of the digestive tract from the lower third of the esophagus to the internal sphincter of the anus and are widely represented in loose connective tissue. Interstitial cells of Cajal are represented by networks associated with the smooth muscles. They have close connections with the nerves that provide innervation. The morphological studies suggest that the functions of ICC in the organs of the digestive tract are as follows:

- generation of slow waves in smooth muscles (described below);
- spread of electrical phenomena in the tissues of organs;
- role of intermediates in neuromuscular transmission.

In patients with chronic slow-transit constipation, which requires surgery due to its resistance to conservative therapy [30], the histology of resected bowel sections showed a significant decrease in the neurons number (due to the phenomenon of apoptosis) and ICC compared to control group, as well as a significant decrease in the number of intestinal glial cells (EGC) in the intermuscular and submucosal plexuses not due to apoptosis [8].

A hypothesis about a disturbance of the gut — brain interactions presents various factors of relevance that include visceral hypersensitivity, abnormalities in sensory/motor function, delayed colonic transit, and altered central perception [6]. Thus, in the instance of OIC, the cause is directly linked to the agonism of opioid receptors in the gastrointestinal tract leading to the reduced intestinal secretion and motility. OIC was introduced as a new diagnosis in the Rome IV disorders of chronic constipation. However, the Rome IV working committee opted to include OIC to help facilitate its recognition and aid further research [24].

Diagnostic methods

Anamnesis vitae, anamnesis morbi, complaints and physical examination are mandatory for evaluation of patients with constipation. The main aim of additional diagnostic procedures is exclusion of anatomic (colonoscopy, barium enema) and extracolonic causes of constipation. The next step is a 6-month conservative treatment, including dietary modifications, physical exercise, behavioral and pharmacological therapy. In case of failure to manage the problem, a referral to colonic and anorectal physiologic testing should be considered.

Chronic constipation is evaluated similarly to any other gastrointestinal complaint. That's why, its organic etiology (i.e., colorectal cancer, inflammatory bowel disease) should be initially excluded. A clinical history, gastrointestinal examination and basic laboratory tests are necessary. Further investigations to diagnose an organic pathology should then depend on whether warning signs are present [48].

If patients had symptoms of chronic constipation in the last 3 months (with the onset of at least 6 months prior to it), and no organic gastrointestinal pathology, they can be categorized according to the Rome IV criteria into one of the following diagnoses [48, 70].

a. Irritable bowel syndrome with constipation (IBS-C) — manifested by abdominal pain at least 1 day per week, where the pain is associated with at least two of the following:

- change in stool frequency → toward infrequent bowel movements;
- change in stool form → toward harder stools;
- related to defecation.

Patients have to report changes, when they have abnormal stools, to detect constipation and diagnose IBS-C.

b. Functional Constipation (FC) — these patients do not fulfill the criteria for IBS, because abdominal pain is absent/not predominant or occurs less than 1 day per week. Patients, who consume opiates, should be excluded from a diagnosis of functional constipation as they rather fit within the realms of opioid-induced constipation.

The symptoms of FC must include two or more of the following:

- straining (more than 25 % of defecations);
- lumpy or hard stools (BSFS type 1 or 2), more than 25 % of defecation;
- sensation of incomplete evacuation (more than one-fourth (25 %) of defecations);
- sensation of anorectal obstruction/blockage (more than one-fourth (25 %) of defecations);
- manual maneuvers to facilitate more than one-fourth (25 %) of defecations;
- fewer than three spontaneous bowel movements per week.

c. Opioid-induced constipation — symptoms of constipation occur after initiating, changing, or increasing opioid therapy.

d. Functional defecation disorders (inadequate defecatory propulsion and dyssynergic defecation) — the criteria for IBS-C or FC, features of impaired rectal evacuation as demonstrated by two of the following three tests:

- abnormal balloon expulsion test;
- abnormal anorectal evacuation pattern with anorectal manometry (or anal surface electromyography (EMG);
- impaired rectal evacuation on defecography, but without structural lesions.

The Bristol Stool Form Scale (BSFS) is a validated tool for stool consistency assessment because stool consistency has been shown to be a more reliable indicator of colonic transit than stool frequency. There are seven types of stools [48]:

- type 1 and 2 — hard or lumpy stool;
- type 6 and 7 — loose or watery stool.

The presence of other gastrointestinal symptoms (e.g., abdominal pain, bloating, and vomiting) or warning symptoms, which include unintentional weight loss, rectal bleeding and a family history of colorectal cancer or inflammatory bowel disease, have to be assessed [1]. Also, we must take into consideration some neurological disorders, such as Parkinson's disease, or medications, such as opiates, calcium channel blockers, and tricyclic antidepressants, that can be manifested by constipation.

According to most studies, straining, hard stools, abdominal discomfort, bloating, infrequent bowel movements, and feeling of incomplete evacuation after bowel movement were frequent symptoms of chronic constipation. [42] Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire or the Bristol stool scale help to provide the clinical evaluation of patients with constipation [6].

The Rome IV criteria include the following symptoms: (a) straining; (b) hard stools (Bristol 1-2); (c) sensation of incomplete evacuation; (d) sensation of anorectal obstruction; (e) need for manual maneuvers to facilitate evacuation; and (f) less than 3 spontaneous bowel movements per week [56].

The authors suggest the application of the 25 % rule (a symptom present in 25 % of stool movements) to all symptoms to facilitate the use of the criteria in the clinical setting [61, 75, 78, 90].

As mentioned in the Rome IV criteria, functional bowel disorders are an only part of the disorders with great overlap in clinical practice. Bloating and abdominal pain are typical for constipated patients. According to the recent recommendations, the diagnosis of IBS should be considered only in patients with abdominal pain [9, 10, 56, 83]. But the problem arises as a result of lack of objective biological markers for FC and IBS-C.

As a side effect of opioid intake, constipation may be observed in 81 % of patients, even if they are concomitantly prescribed laxatives [2]. Due to the increasing use of opioids in Western countries, there is a strong need to rule out the use of opioids in patients with constipation, especially considering that opioid consumption is not always reported by patients [2, 26, 34, 56, 75, 90]. Opioids exert their analgesic effects by crossing the blood — brain barrier and binding to opioid receptors within the central nervous system. Our GI tract is also abundant with opioid receptors and their agonism leads to the reduced intestinal secretion and motility, giving rise to OIC. Indeed, OIC occurs in 51—87 % of patients receiving opioids for cancer and between 41 % and 57 % patients receiving opioids for chronic non-cancer pain [25].

Physical examination

First of all, an organic disease, the presence of abdominal masses and lymphadenopathy, as well as warning signs have to be rule out. According to the existing guidelines, the diagnosis of constipation is mainly made on the basis of symptoms alone [23, 56, 90]. A US survey showed that the most frequent symptoms of chronic constipation were straining, hard stools, abdominal discomfort, bloating, infrequent bowel movements, and feeling of incomplete evacuation after bowel movement.

Anoscopy or colonoscopy should be also provided. A digital rectal examination should be undertaken to palpate for anorectal strictures, hemorrhoids, anal fissures, to assess for perineal descent and anal sphincter relaxation; the presence of parodoxical anal contraction may imply dyssynergic defecation [70]. The sensitivity and specificity of digital rectal examination for dyssynergic defecation is 75 % and 87 %, respectively. So, further confirmation with anorectal manometry is required, and if abnormal findings are obtained, it can be successfully treated with biofeedback.

Laboratory methods

This includes blood tests checking for anemia, inflammation, hypothyroidism, hypercalcemia, and celiac disease [48]. Although celiac disease is commonly perceived as a diarrheal illness, 1 in 10 patients present with constipation [79]. A transabdominal/vaginal ultrasound scan should also be performed in postmenopausal women with recent onset constipation, localized lower abdominal pain, bloating or distension; rarely, ovarian cancer can be the underlying cause.

Instrumental methods

a. For patients with warning symptoms, a colonoscopy or cross-sectional study should be prescribed after clinical evaluation. There is little diagnostic yield of performing a colonoscopy for chronic constipation in those without any alarm features [48]. No association between chronic constipation and the development of colorectal cancer was found [33].

b. The balloon expulsion test is used to asses rectal evacuatory disorder, such as dyssenergic defecation. The test is done by timing how long it takes a patient to evacuate a rectal balloon, filled with either 50 ml of water or air; in health, most will evacuate within 1—2 min. However, there are important considerations for the balloon expulsion test. It can lack sensitivity as the balloon may not mimic the patients' regular stool and thus be evacuated even in those with a defecatory disorder. Some delicate issues also interfere with its specificity as, despite individuals being asked to expel the balloon whilst sitting on a commode behind a private screen, they may still not feel comfortable being outside the confines of their own toileting environment. Finally, an abnormal result cannot differentiate between inadequate defecatory propulsion, dyssynergic defecation, and a structural evacuatory disorder. As such,

the test is commonly performed and interpreted alongside high-resolution anorectal manometry and defecography [70].

c. Anorectal manometry — for patients in whom a functional defecation disorder (inadequate defecatory propulsion and/or dyssynergic defecation), following the initial digital rectal examination or when standard medical therapy has failed [70]. During the anorectal manometry, the rectal propulsive pressure is also assessed to diagnose patients with inadequate defecatory propulsion. Normally, ARM should demonstrate adequate coordination between the increase in intrarectal pressure and anal relaxation. Weak abdominal compression and inadequate relaxation of the anal canal. The recto-anal inhibitory reflex (RAIR) depends on gut innervation. An abnormal RAIR is typically found in Hirschsprung's disease, Chagas disease [72].

The functional defecation disorders can be classified into the manometric subgroups (type I and III describe dyssynergic defecation) that are given below [70].

Type I — Adequate intrarectal propulsive pressure but increased anal sphincter pressure.

Type II—Inadequate intrarectal propulsive pressure and increased anal sphincter pressure.

Type III — Adequate intrarectal propulsive pressure but absent/insufficient anal sphincter relaxation.

Type IV — Inadequate intrarectal propulsive pressure and absent/insufficient anal sphincter relaxation.

The main purpose of functional testing is to determine the pathophysiological mechanisms of constipation and subsequently guide therapeutic measures [71].

Defecography is the most commonly used test before surgical management of constipation/evacuation disorders that aims at reversing demonstrable posterior compartment abnormalities (e.g., rectal prolapse, rectocele, high-grade intussusception), which are consistent with the presentation of symptoms. This radiological procedure dynamically images the rectum and pelvic floor during attempted defecation and also assesses functional parameters (anorectal angle at rest and straining) [70].

Colonic transit studies are indicated for patients after unsuccessful medical conservative treatment, and before surgical intervention planning [20].

Radio-opaque marker testing. Patient should swallow 10 radio-opaque markers per day for six consecutive days, followed by fluoroscopic imaging on the morning of day 7 to count the number of remaining markers; the colonic transit time can then be calculated (in days) by dividing the number of retained markers with the daily dose [65, 86]. This test is useful for the evaluation of oro-anal transit, with the advantages of low cost, simplicity, and wide availability. However, the protocols are not standardized, and the technique varies depending on the center. Usually, STC is characterized by a delayed colonic transit time [72].

None of the tests are sufficient to diagnose a defecation disorder, at least two abnormal evacuation tests are necessary to diagnose a functional defecation disorder (FDD) [70].

Conservative treatment

The first-line management of patients with constipation that is carried out at any level of the healthcare system and according to the existing recommendations [76] is presented in Fig. 1.

The initial treatment of chronic constipation is always conservative and includes basic lifestyle and dietary modifications. There are main principles of conservative treatment for patients with chronic constipation: general health issues, high fiber diet and medications (laxatives and enemas). The general health issues are body training (e.g., jogging, hiking, and gymnastics) and enough fluid intake (at least 1.5—2.0 L/day). Taking into consideration a systematic review and metanalysis of the nine randomized controlled trials, involving 680 participants, physical training can be recommended for chronic constipation as its benefits and feasibility are evidenced by these studies [31]. The effects of exercise may be observed through modulation of anti-inflammatory and anti-oxidative mechanisms [37]. Hence, patients should increase their physical activity as tolerated, starting with a 20-minute walk (e.g., roughly 1 mile) each day. Usually, patients are told to increase their fluid intake. A randomized controlled study in patients with chronic constipation showed that those allocated to 2 L of mineral water per day increased stool frequency compared to the group allocated ad libitum fluid intake (~1 L per day); however, the findings may be confounded by the mineral water containing magnesium [3]. Additionally, patients should be informed that physiological bowel activity is high in the morning after getting up. That is why, patients should use the «gastrocolic reflex» in having enough time after breakfast for evacuation («toilet training»). Some suppositories, which increase rectal contractility, can augment the reflex. The physician should talk to patient in order to identify the patient's concerns and understanding of the disorder. It's very important to involve the patient in treatment decisions rather than issuing directives. This approach improves patient satisfaction and compliance with the prescribed therapy, as well as reduces subsequent physician visits [24].

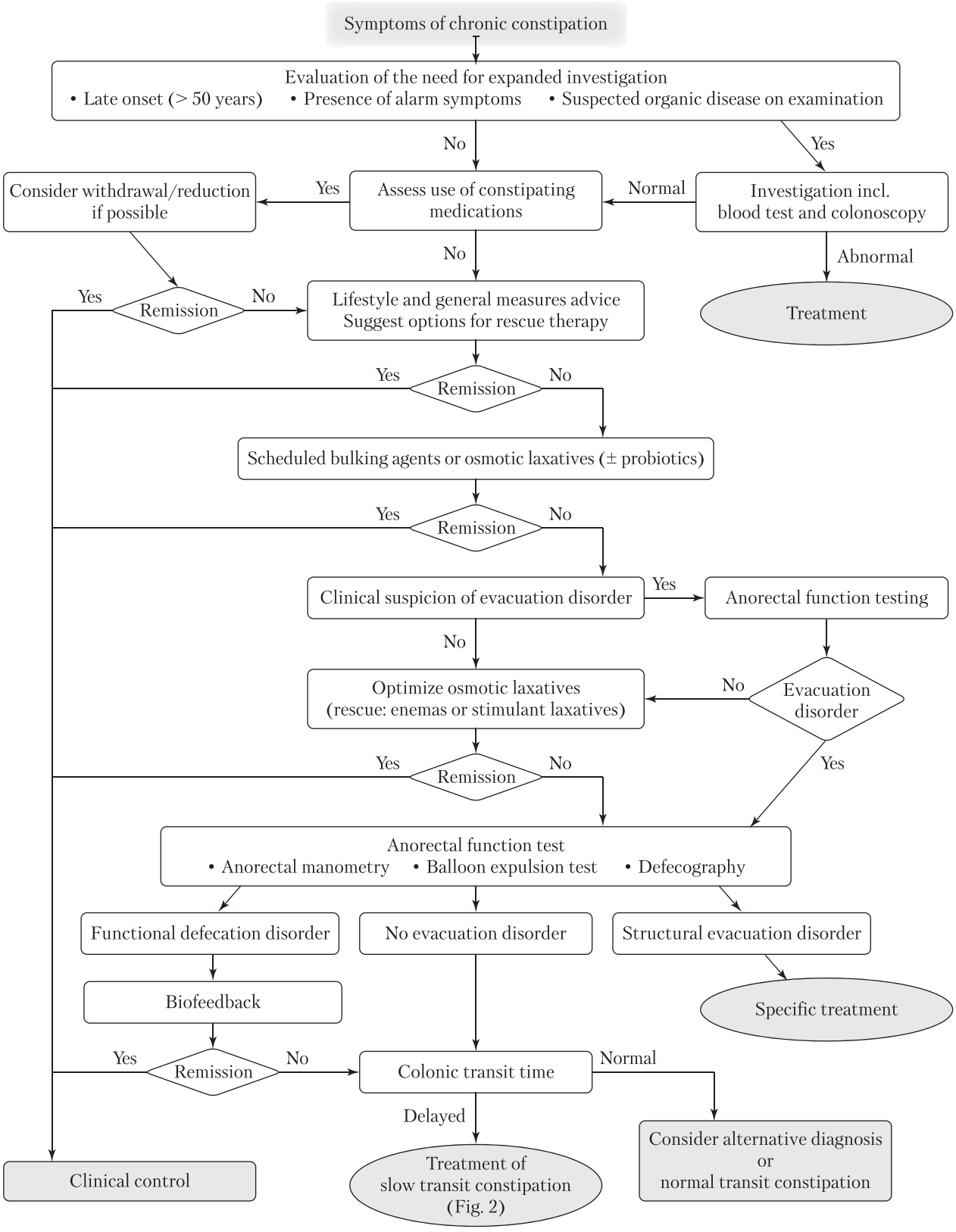

Figure 1. **First-line management of patients presenting with constipation at any level of the healthcare system** [76]. Defined as difficult, unsatisfactory, or infrequent defecation for at least 3 previous months [58]. Rescue therapy may include suppositories or rectal enemas, if accepted by the patient, or the use of fiber or osmotic laxatives upon request. The level of evidence is very low. It is strongly recommended [82]. The use of probiotics seems promising; however, no strong evidence of their effectiveness exists [19]. When available, anorectal function testing may be indicated at this stage when there is a clinical suspicion of an evacuation disorder (manual maneuvers, hemorrhoids, prolapse or rectocele, painful evacuation, etc.) [81]. Alternatively, other treatments, including prokinetics or secretagogues, could be tried

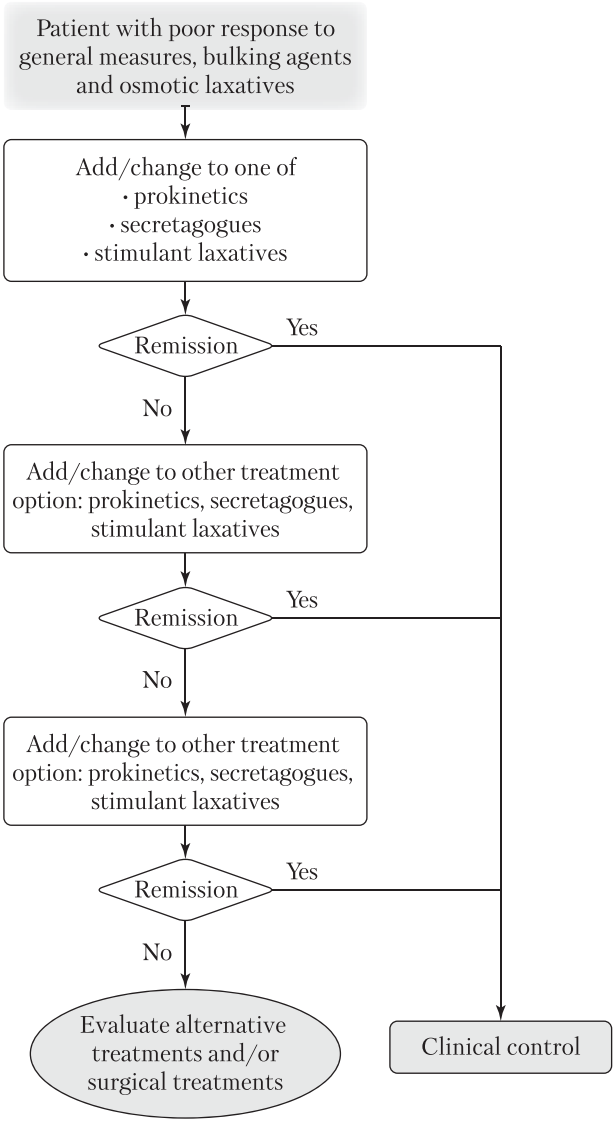

Figure 2. **Treatment of constipation that is not caused by an evacuation disorder and is refractory to first-line management** [76]. The primary choice depends on the patient's characteristics, such as coexistence of abdominal pain or distension, cost/efficacy evaluation, and local pReferences [58]. As a rescue therapy, stimulant laxatives may be used, as well as suppositories, rectal enemas, or rectal irrigation

Supplementing the diet with fiber can be of benefit because it serves to enhance the water holding properties of the stool, form gels to provide stool lubrication, and provide bulk for the stool and stimulate peristalsis.

The American College of Gastroenterology (ACG) issued recommendations, based on these six trials, in which fiber and soluble fiber in particular are considered effective in the management of chronic constipation [28]. The latter appear to relate to the relief of constipation, which further supports the use of soluble fiber in patients with constipation, either FC or IBS-C.

Bulking agents, such as psyllium, bind water and prevent absorption of water from the lumen. It leads to the increased small bowel water content and increased colonic volumes [55]. These effects can explain both positive impacts of bulking agents, resulting in increased stool frequency, and potential side effects, such as bloating, distension, flatulence, and cramping. The presence of adverse effects may limit the use of insoluble fiber, especially if the increased fiber intake is not introduced gradually [28].

Pharmacological treatment

Laxatives. Osmotic laxatives were found to be superior to a placebo for FC first-line treatment according to six randomized controlled trials [29]. Polyethylene glycol was superior to lactulose and non-inferior to prucalopride [5, 22]. A randomized controlled trial demonstrated its superiority over a placebo with regard to the improved stool frequency, stool consistency and straining [17]. Bloating, gas, and loose stools can be dose dependent adverse effects. Stimulant laxatives are also commonly used when osmotic laxative fail in FC patients [28]. According to two relatively recent randomized controlled trials, bisacodyl and sodium picosulphate were found to be superior to a placebo [44, 57]. The most common adverse effects associated with stimulant laxatives are abdominal pain, cramping, and loose stools.

The evidence, supporting the usefulness of saline laxatives, especially polyethylene glycol (PEG), is strong. A few substantial, high-quality trials suggest that PEG works better than a placebo in improving symptoms in patients with chronic constipation [29]. Also, PEG is proved to be superior to lactulose in patients with chronic constipation, resulting in more frequent and looser stools, and less abdominal pain according to a Cochrane review. PEG also increases the number of spontaneous complete bowel movements, improves stool consistency, and reduces severity of straining, without clearly affecting abdominal pain, in patients with IBS-C. The most common side effects with PEG are diarrhea and abdominal pain.

Only some clinical experience maintains the benefits of osmotic laxatives in patients with chronic constipation. Moreover, side effects, such as abdominal cramping and bloating, limit clinical usefulness of the unabsorbed mono/disaccharides, sugar alcohols, lactulose, lactitol, mannitol, and sorbitol. In a randomized controlled trial, dried plums (containing sorbitol, which acts as an osmotic laxative, dietary fibers and polyphenols) were found to be useful, palatable and more effective than psyllium for the treatment of mild-to-moderate constipation [4].

If osmotic laxatives fail, stimulant laxatives are commonly used [28]. Bisacodyl and sodium picosulphate were proved to be superior to a placebo [44]. Abdominal pain, cramping, and loose stools were the most common side effects.

Luminally acting prosecretory agents have been evaluated in patients with either FC or IBS-C, where they can be used as a second-line therapy after standard laxatives. Linaclotide and Plecanatide, guanylate cyclase-C agonists were included in this group. Activation of this receptor on colonic epithelial cells leads to the increased intracellular production of cyclic guanosine monophosphate. Dual action was observed for these laxatives, comprising salt and water secretion into the intestinal lumen, and attenuation of visceral afferent pain signaling. Additionally, linaclotide and plecanatide improve stool consistency and frequency, and reduce abdominal pain. According to the randomized controlled trials, these laxatives demonstrated their superiority compared to a placebo in the treatment of FC and IBS-C [12, 18, 50, 68, 69]. The most common side effect was diarrhea in up to 20 % of patients. Lubiprostone is a chloride-channel activator that stimulates intestinal fluid secretion. Lubiprostone was proved to be better than a placebo and relieved the symptoms of FC and OIC. The good effect was seen at 1 month but was no longer significant at 3 months [51,41]. Diarrhea and nausea were the most common side effects (~8 %).

$5HT_4$ agonists (prucalopride). Serotonin (5-hydroxytryptamine, 5-HT) accelerates gastrointestinal motility, and Prucalopride provides its effect through being a $5HT_4$ receptor agonist. Analyzing six randomized controlled trials, prucalopride was proved to be superior to a placebo in patients with functional constipation and OIC toward achieving at least 3 spontaneous bowel movements per week. Common side effects included diarrhea and headache, but the symptoms normally disappeared within the first week of treatment [15].

Peripherally acting mu-opioid receptor antagonists (PAMORAs). PAMORAs (i.e., nalexagol, naldemedine, methylnaltrexone) reduce the symptoms of OIC by blocking the mu-opioid receptors within the GI tract, but as they do not cross the blood–brain barrier, they neither diminish the central analgesic effect of opioids nor induce withdrawal symptoms. PAMORAs were found to be superior to a placebo in the treatment of OIC [54]. According to a recent European expert consensus statement, PAMORAs have to be prescribed if standard laxatives fail. Prucalopride and lubiprostone in OIC patients can be prescribed after standard laxatives but before PAMORA [6].

Future therapies

Japan is the only country that has approved the drug for the treatment of chronic constipation. Elobixibat is an ileal bile acid transporter inhibitor. It induces a state of bile acid malabsorption, thereby increasing the colonic bile acid pool and leading to increased stool frequency and looser stool consistency. A randomized, double-blind, placebo controlled, phase 3 trial and an open label, single arm, phase 3 trial conducted in Japan found that elobixibat resolved the symptoms of FC in a short period of time, and was well tolerated during both a short and long-term treatment [59].

Anorectal biofeedback

Biofeedback is a training technique that can be used effectively to manage individuals with dyssynergic defecation. This technique can also improve slow transit constipation as a secondary phenomenon to dyssynergic defecation. According to the randomized controlled trials, biofeedback seems to be superior to a standard therapy (i.e., laxatives) for dyssynergic defecation [21, 40]. Home-based biofeedback improves bowel symptoms and its physiology is similar to office-based biofeedback according to a recent randomized controlled trial [73].

Transanal irrigation

Transanal irrigation is useful in patients with a neurogenic bowel dysfunction. It is also indicated for patients with FC in whom pharmacological therapies have failed before surgery. Transanal irrigation can improve bowel function and the quality of life, but more than one third of patients continue their treatment within the first year [43].

Nerve stimulation

Sacral nerve stimulation is an invasive surgical procedure with high morbidity rates (due to displacement, pain, wound infection, and hematoma) ranging between 13 % and 34 % [64]. It was initially indicated for patients with refractory cases of chronic constipation with treatment success ranging between 57 % and 86 %. Thus, sacral nerve stimulation for refractory chronic constipation is an expensive, invasive procedure which lacks proven benefit [6].

Colonic surgery

Sir William Arbuthnot Lane was the first to propose surgical treatment of constipation [49]. The treatment methods of resistant constipation remained

unchanged for many years; surgery was a method of despair; it was indicated when conservative management failed. The indications for surgical treatment, its extent, the timing of conservative treatment and the criteria for evaluating its effectiveness were not clearly defined for a long time [11].

According to the scientific reviews, patients with slow-transit constipation, refractory to a medical therapy and not associated with pelvic outlet obstruction or functional problems, demonstrate sufficient rates of clinical improvement (50 %–100 %) after total abdominal colectomy with ileorectal anastomosis (TA CIRA), as compared with a segmental colon resection, after which failure rates for the treatment of slow-transit constipation can be as high as 100 % [47], [87]. Morbidity after TA CIRA includes anastomotic leak (1 %–11 %), bowel obstruction (8—33 %) [63], and prolonged postoperative ileus (24 %). Laparoscopic TA CIRA also demonstrated great results [35]. Although constipation generally improves after TA CIRA for slow-transit constipation, patients may experience diarrhea, abdominal pain, fecal incontinence, and recurrent constipation [63]. Despite this, > 90 % of patients reported that they would undergo TA-CIRA again to treat their constipation [27].

Thus, colonic resections (i.e., ileorectal anastomosis or ileostomy) are rarely indicated and should only be considered as a last resort in patients with intractable FC, in whom there is clear evidence of slow transit and where pharmacological therapies have failed despite being of optimal dosage and duration. The evidence of benefit of colonic resections is derived almost exclusively from observational studies. A systematic review of 40 articles, providing outcome data in 2045 patients, reported that colectomy may benefit some patients with FC but at the cost of substantial short-and long-term morbidity. Complications occurred in 25 % of patients. Recurrent episodes of small bowel obstruction were observed in about 15 % of patients in the long term, with significant burden of rehospitalization and frequent recourse to surgery. Hence, current evidence is insufficient to guide patient or procedural selection [46]. Moreover, it should be avoided in those with panenteric dysfunction, and neither does it have a role in IBSC, OIC or dyssynergic defecation.

Conclusions

Chronic constipation is still considered a functional or idiopathic disorder. However, there is recent evidence that its pathophysiological grounds may be actually due to a complex system of abnormalities of the enteric nervous system of these patients. In particular, as reported in this review, the enteric glial cells seem to be constantly involved in constipated patients, suggesting that (at least some forms of) constipation should be considered as true neuro-gliopathies.

The last decade has seen an increase in the repertoire of pharmacological therapies available for the treatment of chronic constipation. By adopting a logical step-wise approach toward the diagnosis of chronic constipation and its individual subtypes, clinicians have the opportunity to tailor a therapy accordingly and improve symptoms, the quality of life, and patient satisfaction.

Despite numerous publications on slow transit constipation, the latter is still the subject of research for many specialists. The literature review indicates that surgery still remains the most radical treatment method for patients with slow transit constipation. A lot of recent scientific works have been dedicated to the immunohistochemical studies of interstitial pacemaker cells. The numbers of markers they express were found. Consequently, the investigations of modern scientists are aimed to develop and implement new laboratory methods for determining the indications for surgical treatment depending on a diagnosed disorder of the intestinal neurophysiology. These methods will ensure a differentiated selection of patients for surgical treatment.

Declaration of interests

We declare no competing interests. The authors are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Author contributions

I. M. Leshchyshyn, Y. M. Susak, L. Y. Markulan: project idea and revision of its drafts; O. I. Okhots'ka, P. L. Byk: search and selection of literary sources, writing this review, making edits; O. V. Panchuk: help with finding literary sources.

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Хронічні запори: сучасний погляд на проблему. Огляд літератури

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Хронічний запор є поширеною гетерогенною патологією, що трапляється та значно погіршує якість життя в усіх групах населення. Її частота збільшується з віком. Це зумовлено малорухливим способом життя, недостатньою кількістю харчових волокон і рідини в раціоні, широким спектром захворювань, які безпосередньо призводять до розвитку хронічного запору, інтеркурентних захворювань, зловживанням проносними або комбінацією зазначених чинників. Хронічні запори уражають приблизно 10—15 % дорослого населення, значно погіршуючи якість життя. Оскільки є велика кількість розладів, що призводять до запорів, існують численні класифікації останніх, заснованих, зазвичай, на їхній етіології або механізмах. Для точної класифікації запорів використовуються різні критерії, але все ще важко знайти одну класифікацію, яка б охоплювала всі типи. Римські критерії IV класифікували розлади хронічного запору на чотири підгрупи. Лікування залежить від підтипу. Незважаючи на наявність публікацій, присвячених повільнотранзитним запорам, останні є предметом вивчення для багатьох фахівців у різних наукових галузях. Останніми роками багато наукових праць було присвячено імуногістохімічним дослідженням інтерстиціальних пейсмейкерних клітин. Виявлено маркери, які вони експресують. Головною метою сучасних вчених є розробка та впровадження нових лабораторних методів, які б остаточно визначили показання до хірургічного втручання з урахуванням виявлених порушень нейрофізіології кишечника і дали змогу диференційовано відбирати хворих для оперативного лікування. Поетапний підхід до діагностики хронічного запора дає змогу вибрати адекватний метод лікування з метою поліпшення симптомів та якості життя і підвищення задоволеності пацієнтів. Підсумовуючи огляд літератури з цієї проблеми, можна дійти висновку, що хірургічне втручання залишається найбільш радикальним методом лікування пацієнтів із повільнотранзитними запорами.

Ключові слова: повільнотранзитний запор, проносні, тотальна колектомія, ілеоректоанастомоз.

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Leshchyshyn IM, Susak YM, Okhots'ka OI, Byk PL, Markulan LY, Panchuk OV. Chronic constipation: modern view on the problem. General Surgery (Ukraine). 2021:1;67-79. http://doi.org/10.30978/GS-2021-1-67.

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Acknowledgements (not obligatory). Acknowledge those who contributed to the manuscript providing technical help or writing assistance, or who provided general support.

Author contributions. Participation of each author in the manuscript writing (concept and design of the study; material collection, material processing, statistical data processing, writing text, and etc.)

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Funding. All sources of funding must be acknowledged in the manuscript.

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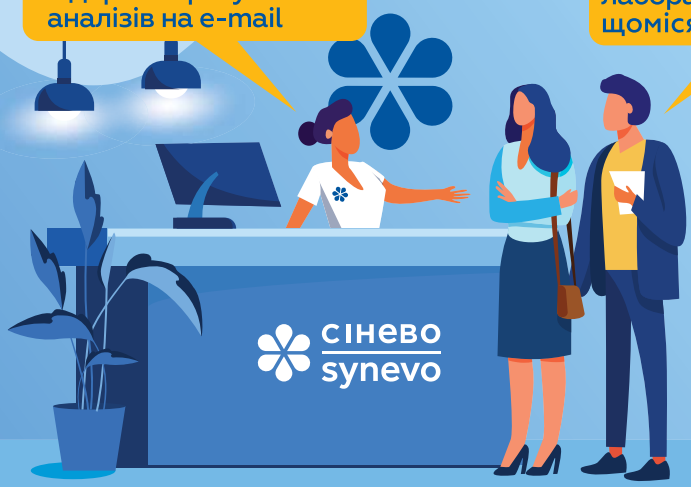

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