

**OPTIMIZATION OF METHODS OF PREVENTION OF ACUTE PANCREATITIS  
DURING TRANSPAPILLARY ENDOSCOPIC INTERVENTIONS IN PATIENTS WITH  
BILIARY TRACT DISEASES COMPLICATED BY MECHANICAL JAUNDICE**

**MEXANIK SARIQLIK BILAN MURAKKABLASHGAN O'T YO'LLARI KASALLIKLARI  
BO'LGAN BEMORLARDA TRANSPAPILLYAR ENDOSKOPIK ARALASHUVLARDA  
O'TKIR PANKREATITNING OLDINI OLIISH USULLARINI OPTIMALLASHTIRISH**

**ОПТИМИЗАЦИЯ МЕТОДОВ ПРОФИЛАКТИКИ ОСТРОГО ПАНКРЕАТИТА ПРИ  
ТРАНСПАПИЛЛЯРНЫХ ЭНДОСКОПИЧЕСКИХ ВМЕШАТЕЛЬСТВАХ У  
ПАЦИЕНТОВ С ЗАБОЛЕВАНИЯМИ ЖЕЛЧЕВЫВОДЯЩИХ ПУТЕЙ,  
ОСЛОЖНЕННЫМИ МЕХАНИЧЕСКОЙ ЖЕЛТУХОЙ**

*Rayimov Gayrat Nabiyevich - DSc, Prof.  
Kholmukhamedov Jasurbek Rakhmatjon oqli  
Central Asian Medical University*

*E-mail: dr.rayimov.gayrat@gmail.com, Tel: (+998) 97 944-30-03*

*Abdullaev Mukhamaddali Khalimovich - Private clinic "Endomed+"*

*Kosimov Sherzodbek Khursanali oqli - Fergana medical institute of public health*

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**Abstract:** Accurate diagnostics and treatment of diseases of the pancreas (PG), gallbladder (GB) and bile ducts are one of the most important tasks of modern gastroenterology and hepatopancreatobiliary surgery. Endoscopic retrograde cholangiopancreatography (ERCP) remains an indispensable method of early diagnostics and minimally invasive treatment of various diseases of the pancreatobiliary system (PBS), which has entered clinical practice since the late 1960. This article presents an analysis of the results of endoscopic interventions on the major duodenal papilla and common bile ducts in 142 patients with complicated cholelithiasis (CSD) for the period from 2015 to 2020. It has been proven that intravenous drip administration of octreotide 600 mcg/ day for the prevention of acute post-manipulation pancreatitis during endoscopic interventions on the major duodenal papilla and common bile ducts is more effective than the traditional form of its use.

**Key words:** transpapillary endoscopic interventions, acute post-manipulation pancreatitis, prevention, octreotide, cholelithiasis.

**Annotatsiya:** Oshqozon osti bezi, o't pufagi va o't yo'llari kasalliklarini aniq tashxislash va davolash zamonaviy gastroenterologiya va gepatopankreatobiliar jarrohlikning eng muhim vazifalaridan biridir. Endoskopik retrograd xolangiopankreatografiya (ERXPG) 1960-yillarning oxiridan beri klinik amaliyotga kirgan pankreatobiliar tizimning turli kasalliklarini erta tashxislash va mini-invaziv davolashning ajralmas usuli bo'lib qolmoqda. Ushbu maqolada 2015 yildan 2020 yilgacha bo'lgan davrda 142 nafar asoratlangan xolelitiaz (KSD) bilan og'rigan bemorlarda o'nikkibarmoq ichakning katta so'rg'ichi va umumiy o't yo'llarida endoskopik aralashuvlar natijalari tahlili keltirilgan. O'nikkibarmoq ichak va umumiy o't yo'llarida endoskopik aralashuvlar jarayonida 600 mkg/sut Oktreotidni tomir ichiga tomchilab yuborish o'tkir post-manipulyativ pankreatitning oldini olish uchun an'anaviy foydalanish shaklidan ko'ra samaraliroq ekanligi isbotlangan.

**Kalit so'zlar:** transpapilyar endoskopik aralashuvlar, o'tkir postmanipulyativ pankreatit, profilaktika, oktreotid, xolelitiaz.

**Аннотация:** Точная диагностика и лечение заболеваний поджелудочной железы (ПЖ), желчного пузыря (ЖП) и желчных протоков являются одной из наиболее важных задач современной гастроэнтерологии и гепатопанкреатобилиарной хирургии. Незаменимым методом ранней диагностики и миниинвазивным способом лечения различных заболеваний органов панкреатобилиарной системы (ПБС), вошедшим в клиническую практику с конца 60-х гг. прошлого века, остается эндоскопическая ретроградная холангиопанкреатография (ЭРХПГ). В данной статье приводится анализ результатов эндоскопических вмешательств на большом сосочке двенадцатиперстной кишки и общих желчных протоков у 142 пациентов с осложненной формой желчнокаменной болезни (ЖКБ) за период с 2015 г. по сентябрь 2020 г. Доказано, что внутривенное капельное введение октреотида 600 мкг/сут с целью профилактики острого постманипуляционного панкреатита при эндоскопических вмешательствах на большом сосочке двенадцатиперстной кишки и общих желчных протоках является эффективнее, по сравнению с традиционной формой его использования.

**Ключевые слова:** транспиллярные эндоскопические вмешательства, острый постманипуляционный панкреатит, профилактика, октреотид, желчнокаменная болезнь.

**Introduction.** In addition to diagnostics, ERCP allows for a variety of surgical manipulations, which in some situations are a worthy alternative to traditional surgical interventions [4-6]. At the same time, ERCP itself with manipulation on such a complex anatomical structure as the major duodenal papilla (MDP) carries the risk of developing serious and dangerous complications. Their frequency increases with the use of “aggressive” methods: extended and atypical (non-cannulation) endoscopic papillosphincterotomy (EPST), lithotripsy, bougienage, dilation of strictures of the terminal section of the common bile duct (CBD), as well as endoscopic prosthetics methods [2-6].

**Literature review.** According to Tulin et al. 2007, a post-manipulation pancreatitis (APMP) is considered a severe complication of endoscopic interventions on the common bile duct and pancreatic duct (PD), characterized by a variety of clinical manifestations and treatment outcomes. In the prevention and treatment of acute post-manipulation pancreatitis (APMP), the main attention is paid to pharmacological methods of blocking the exocrine function of the pancreas, since the processes of enzymatic autolysis in combination with vascular lesions are the leading ones in the genesis of its damage. The most important place among the drugs used for this purpose belongs to antisecretory drugs, among which the most effective to date is an analogue of the natural regulator of the exocrine function of the pancreas hormone somatostatin - octreotide [7, 8, 9]. However, for various reasons, information on the effectiveness of using the drug as a preventive measure for the development of APMP during ERCP and other endoscopic manipulations remains highly contradictory [5-8, 10, 12].

The high incidence of APMP development after ERCP, as well as the lack of effective methods for preventing its development, determine the high relevance of studying risk factors and developing new approaches that increase the safety and effectiveness of endoscopic treatment methods for benign diseases of the biliary tract. To date, issues of drug prevention of APMP after surgical endoscopy have not been fully resolved and require further development.

**The aim of the study** was to investigate the possibilities of intravenous drip administration of octreotide 600 mcg/ml during ERCP, endoscopic interventions on the common bile duct and the major gastrointestinal tract, to determine the scope of drug prophylaxis and to identify risk factors for the development of acute pyelocaliceal reflux disease.

**Material and research methods.** A retrospective analysis of the results of endoscopic interventions on the MDP and CBD was conducted in 142 patients with complicated cholelithiasis for the period from 2015 to 2020 at the Endomed + clinic, located in Fergana, Fergana region, Republic of Uzbekistan. The inclusion criteria for the study were patients with uncomplicated cholelithiasis, choledocholithiasis, as well as patients with mechanical jaundice and cholangitis. The age of the subjects was from 20 to 70 years. Exclusion criteria: patients under 20 or over 70 years old; cholelithiasis and choledocholithiasis, mechanical jaundice against the background of oncological diseases of the liver, duodenum, MDP, bile ducts and gallbladder; acute pancreatitis and (or) pancreatic necrosis at the time of endoscopic intervention or during hospitalization of the patient; development

of bleeding from the papillotomy area, cholangitis, acute cholecystitis after ERCP. Among the studied subjects, there were 88 women (62%) and 64 men (45%). The age of the patients ranged from 22 to 69 years (mean age  $62.3 \pm 2.1$  years). A total of 57 patients (40.14%) with clinical and laboratory manifestations of complicated cholelithiasis (choledocholithiasis, mechanical jaundice, cholangitis) were urgently hospitalized, while 85 patients (59.9%) were admitted on a planned basis. All patients were divided into two groups: the main group included 67 patients, and the comparison group included 75. Group 1 (main) included 22 men and 45 women, while Group 2 (comparison) included 25 men and 50 women. The study groups were comparable in terms of age, gender, CBD diameter (based on ultrasound results), the number of patients with jaundice at admission and with normal direct bilirubin levels, the frequency of complex cannulation of the MDP, the performance of typical and suprapapillary (atypical) papillotomy, and contrast of the CBD during ERCP.

Patients of the 1st group were administered 600 mcg of octreotide diluted in 60 ml of 0.9% sodium chloride (NaCl) solution intravenously by drip as drug prophylaxis against APMP the day before the study, and on the day of endoscopic intervention, the same method and the same volume of the drug were administered in fractional doses of 200 mcg 3 times using an infusion pump. Prevention of APMP in patients of the 2nd group was performed using subcutaneous administration of 100 mcg of octreotide the day before ERCP and subsequent three-time subcutaneous injections of 100 mcg of octreotide on the day of the study.

In the 1st group, 20 (29.9%) patients (6 men and 14 women) were admitted on an emergency basis, and 47 (70%) patients (20 men and 30 women) were admitted on a planned basis. In the 2nd group, out of 75 patients, 23 (30.7%) patients (7 men and 16 women) were hospitalized on an emergency basis, and 52 (69.3%) patients (22 men and 30 women) sought planned medical care.

Of the 142 patients admitted for inpatient treatment, 102 (50 in the 1st group and 52 in the 2nd) had a clinical diagnosis of cholelithiasis, chronic cholecystitis, and choledocholithiasis. In 31 patients (14 in the 1st group and 17 in the 2nd), cholelithiasis, chronic cholecystitis, choledocholithiasis, and mechanical jaundice were diagnosed. In addition to cholelithiasis, chronic cholecystitis, choledocholithiasis, and mechanical jaundice, 17 more patients (8 in the 1st group and 9 in the 2nd) had signs of cholangitis. The level of direct bilirubin in the blood at the time of hospitalization ranged from 62 to 295 mmol/l ( $124.7 \pm 13.9$  mmol/l). Duration of jaundice up to 3 days were observed in 27 (26.5%) patients, more than 3 days - in 15 (14.7%), more than 7 days - in 8 (7.8%) patients.

All hospitalized patients underwent ERCP on days 1–3 with varying volumes of intervention on the MDP and CBD (EPS and lithoextraction; EPSS and internal or external drainage of the CBD). All interventions were performed by one specialist with extensive experience in endoscopic manipulations on the MDP and CBD.

The standard scheme of patient preparation for the study included at least 6 hours of complete fasting. Before ERCP, all patients received the following premedication. 30 min before — atropine sulfate 0.1% 1.0 ml intramuscularly, diphenhydramine 1% 1.0 ml intramuscularly, promedol 2% 1.0 ml intramuscularly, droperidol 0.25% 2.0 ml intramuscularly. The purpose of premedication was to improve conditions for endoscopy of the upper gastrointestinal tract, selective cannulation of the common bile duct and surgical intervention on the MDP, and to create a favorable psychoemotional background for the patient before ERCP.

Depending on the objectives of the study and the nature of the disease, 10 to 20 ml of a 30% solution of a contrast agent (Ultravist-300) were slowly injected into the bile ducts under fluoroscopic control, the obtained cholangiograms were analyzed, and the anatomical conditions for performing EPST and other endoscopic manipulations on the BSP and CBD were assessed.

After EPST, revision of the CBD was performed using Dormia baskets. In the absence of conditions for lithoextraction (“difficult” CBD stones), internal endoprosthetics of the CBD or external nasobiliary drainage were performed as a temporary measure to decompress the bile ducts and prevent stone impaction.

After ERCP and other endoscopic manipulations on the MDP and CBD, the patients were prescribed infusion therapy: 2% papaverine 2.0 ml in 400 ml of 0.9% NaCl solution, no-shpa 2.0 ml in 400 ml of 0.9% NaCl solution, 4% potassium chloride 30 ml in 400 ml of 5% glucose solution.

Additionally, hypothermia of the epigastric region was performed (ice pack) and octreotide was prescribed. Dynamic observation of the patients' condition was carried out, complaints were assessed. In the development of APMP, treatment was carried out based on the methodological recommendations of the IX Conference of Surgeons-Hepatologists of Russia and the CIS Countries (2002), the XIV International Congress of Surgeons-Hepatologists of the CIS Countries "Actual Problems of Surgical Hepatology" (2007).

The following parameters were analyzed: serum amylase activity, duration of hyperamylasemia, and the presence of a relationship between hyperamylasemia and the (possible) prognostic factor under study. Normal serum  $\alpha$ -amylase activity was considered to be 12–32 mg/ml per hour. The first assessment of amylase activity was performed on the day of the study. In the presence of clinical manifestations of acute pancreatitis, serum  $\alpha$ -amylase activity was monitored earlier.

**Results.** In the 1st group, the following endoscopic interventions were performed: ERCP, EPST, and lithoextraction — in 50 (74.6%) patients, ERCP, EPST, and internal endoprosthetics of the CBD — in 6 (9%) patients, ERCP, EPST, and external nasobiliary drainage of the CBD — in 11 (16.4%) patients. In the 2nd group, these endoscopic manipulations were performed in 54 (72%), 6 (8%), and 15 (20%) patients, respectively. Difficulties in cannulation of the MDP were noted in 26 (38.8%) patients of the 1st group and in 30 (40%) patients of the 2nd group, contrasting of the PPC was recorded in 15 (22.4%) and 20 (26.7%) patients, respectively.

After ERCP and other endoscopic manipulations in the 1st group, APMP developed in 9 (13.4%) patients, transient amylasemia - in 12 (17.9%), in the 2nd group - in 14 (18.7%) and 16 (21.3%) patients, respectively. In the remaining patients of the 1st (68.7%) and 2nd (60%) groups, there were no clinical and laboratory manifestations of APMP and transient amylasemia. There were no fatal outcomes.

In the development of APMP, the most frequent clinical manifestation of the disease was pain syndrome, which was usually intense, without "light" intervals. The most typical localization of pain was the epigastric region, above the umbilical ring. Usually, the pain radiated along the costal margin towards the back, sometimes to the lower back, chest and shoulders, to the left costovertebral angle. Often, the pain syndrome was of a girdle nature. The duration of the pain syndrome varied from several hours to several days. During examination of the abdomen, its distension was noted, mainly in the upper sections. In severe situations, the abdomen was uniformly distended and painful. With deep palpation, the pain sharply increased. During palpation of the lumbar region, especially the left costovertebral angle, severe pain arose (Mayo-Robson symptom). In most observations of APMP, resistance of the anterior abdominal wall was determined in the absence of symptoms of peritoneal irritation.

Peritoneal symptoms appeared much later and were usually associated with the presence of exudate in the abdominal cavity. Transverse painful resistance of the anterior abdominal wall in the projection of the pancreas (Kerte's symptom) was often observed. Almost simultaneously with the pain, the appearance of repeated, painful and unrelieved vomiting was noted. In some patients, intestinal paresis was observed, which was most often barely noticeable, but sometimes very pronounced, up to the development of dynamic intestinal obstruction. When the body temperature increased, it was often subfebrile. In the 2nd group, a greater number of patients experienced pain, nausea and vomiting (34 and 19%, respectively).

The following factors were selected for analysis as factors that presumably influence the development of APMP: patient age, volume of drug premedication, patient gender, diameter of the CBD according to ultrasound data, direct bilirubin level, complexity of cannulation of the MDP, performance of atypical (suprapapillary) EPST, administration of a contrast agent into the CBD during ERCP.

The Student's t-test showed that there were statistically significant differences in the mean values of the duration and level of hyperamylasemia. In the 1st group, compared with the 2nd group, the amylase level ( $p < 0.005$ ) and duration of amylasemia ( $p < 0.016$ ) were statistically significantly

smaller. These results were confirmed by the nonparametric Mann-Whitney test, which was also used to compare two independent samples of equal size.

It is also necessary to note the convenience of using the new dosage form — octreotide 600 mcg — in the 1st group of patients, which made it possible to obtain a daily dose of the drug by a single intravenous injection. No side effects were observed with the new dosage form — octreotide 600 mcg. It is important to note that in the 1st group of 8 patients with developed APMP, pancreatic necrosis was not diagnosed in any observation, whereas in the 2nd group of 13 patients with APMP, pancreatic necrosis developed in 2 patients.

**Discussion.** It is traditionally believed that APMP is acute pancreatitis developing within 24 hours after ERCP and accompanied by an increase in the serum alpha-amylase level by 3 or more times compared to the maximum allowable value. In the pathogenesis of APMP after ERCP, the leading role belongs to a sharp increase in pressure in the LPC. This may be associated with trauma to the sphincter of Oddi with subsequent persistent spasm of smooth muscles and the development of edema or excessive administration of a contrast agent into the LPC. Among other mechanisms causing intra-acinar activation of proteolytic enzymes, reflux of bile into the LPC is called. Reflux can also be a consequence of rough manipulations, dysfunction of the sphincter of Oddi, or blockage of the duct system with stones, which leads to disruption of the normal passage of bile and pancreatic secretions. In addition to the impact of the chemical factor, the risk of infection of the pancreatic tissue increases with reflux. Bacteria, their wall components and toxins are capable of causing a local inflammatory response and the release of inflammatory mediators, which can cause intra-acinar activation of proteolytic enzymes with subsequent development of OPMP [11, 12].

During the clinical study, from the standpoint of evidence-based medicine, it was established that such factors as the complexity of cannulation of the MDP, the implementation of atypical papillotomy, and the introduction of a contrast agent into the PJ increase the risk of developing APMP after ERCP. With increasing patient age, on the contrary, the frequency of developing APMP and transient hyperamylasemia after ERCP decreases. At the same time, no relationship was noted between the risk of developing APMP and the patient's gender or the level of direct bilirubin.

After ERCP and other endoscopic manipulations, APMP and transient hyperamylasemia developed in 11.1 and 16.7% of patients in Group 1, respectively. In Group 2, which used the standard octreotide administration regimen (100 mcg subcutaneously before the study and 100 mcg subcutaneously 3 times a day after ERCP), APMP and transient hyperamylasemia were noted in 16.7 and 19.2% of patients.

**Conclusion.** The performance of ERCP, EPST and other endoscopic manipulations requires special measures to prevent APMP. Intravenous drip administration of octreotide 600 mcg/ day for the purpose of preventing APMP during endoscopic interventions on the MDP and CBD is more effective and convenient than the traditional form of its use. Risk factors for the development of APMP during ERCP and other endoscopic manipulations on the MDP and CBD are the young age of the patient, difficulties in cannulation of the MDP, performance of atypical EPST, and the introduction of a contrast agent into the PP.

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