PREVENTION OF POST-ERCP PANCREATITIS IN HIGH-RISK PATIENTS

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ABSTRACT — AIM. To study the efficacy of thoracic epidural analgesia (TEA) for the prevention of post-ERCP pancreatitis in high-risk patients.
MATERIALS AND METHODS. A parallel, blinded, randomized study. The first (TEA group) group included patients (n = 98) in whom thoracic epidural analgesia was used during endoscopic transpapillary interventions (ETI), the second (OAI group) group included patients (n = 97) in whom opioid analgesics and indomethacin (per rectum). RESULTS. The study showed that acute pancreatitis was diagnosed significantly less frequently in patients with the TEA group than in patients with the OAI group (p = 0.0135). If in the TEA group post-ERCP pancreatitis (PEP) was verified in 3.1% (3/98) patients, in the OAI group — in 12.4% (12/97) patients.
When TEA was used in high risk patients of developing post-ERCP pancreatitis, its incidence decreased from 23.3% (10/43) to 4.4% (2/46) observations (p = 0.0095). CONCLUSION. The use of TEA is an effective and justified method of prevention in patients at high risk of developing post-ERCP pancreatitis. In patients with a low risk of developing this complication, the use of TEA is inappropriate due to the invasiveness of the method.

KEYWORDS — therapeutic ERCP (endoscopic retrograde cholangiopancreatography), prevention of post-ERCP pancreatitis, thoracic epidural analgesia.

INTRODUCTION

The use of endoscopic transpapillary interventions (ETI) to correct biliary hypertension syndrome has significantly improved the results of treatment in patients with pathology of the duodenopancreatobiliary zone.

At the same time, ETI are complex interventions with unpredictable consequences. During the perioperative period, severe and sometimes fatal complications may occur, such as post-ERCP pancreatitis (PEP), bleeding from the papillotomy area, and retroduodenal perforation [1, 2, 3, 4].

According to many researchers, the incidence of post-ERCP pancreatitis is within 1–40% of observa-

tions and depends on many factors: the nature of the disease, the type of endoscopic intervention, the patient's age [2]. Such factors as young age, sphincter of Oddi dysfunction, the use of balloon dilatation for ETI, the absence of jaundice increase the risk of its development [3, 5, 6, 10]. To date, mortality in post-ERCP pancreatitis reaches 3–10%, and with developing infected pancreatic necrosis can reach 25–80% of cases [1, 2, 7, 8, 11].

In recent years, there have been positive responses from the research community on the effectiveness of non-steroidal anti-inflammatory drugs (diclofenac and indomethacin) and thoracic epidural analgesia for the prevention of PEP in ETI [1, 12]. Thus, we decided to conduct a comparative analysis to test the effectiveness of these two methods of preventing post-ERCP pancreatitis in high-risk patients.

MATERIALS AND METHODS

Our parallel, unblinded, randomized study was approved by Volgograd Regional Ethics Committee. All participants signed an informed consent.

223 ETI were conducted from January 2019 to December 2020. All patients were hospitalized. In 13 (4.9%) patients, endoscopic intervention was performed for diagnostic purposes (excluded from the study). In 9 out of 223 (4.0%) patients, signs of acute pancreatitis were diagnosed before the intervention (excluded from the study). One patient refused to participate in the study. A total of 200 patients were included in the study.

Prior to the formation of the database, the study design, inclusion and exclusion criteria were determined.

Inclusion criteria:
1. Completed therapeutic ETI;
2. Prior to ETI, the patient had no clinical signs of acute pancreatitis.

Exclusion criterion: a complication (retroduodenal perforation, massive bleeding, detachment of the Dormia basket) was diagnosed during ETI and required an urgent surgical intervention.

All subjects were divided into two groups (100 patients each). The first (TEA group) group included patients in whom TEA was used during ETI, the patients of the second (OAI group) group received a narcotic analgesic and indomethacin.

Puncture and catheterization of the epidural space was performed according to the standard tech-

nique at the level of the VII–VIII thoracic vertebrae. 20 minutes before ETI, a solution of ropivacaine 0.5% – 10 ml was injected into the epidural space.

In the TEA group, two patients were excluded from the study due to unsuccessful attempts to insert a catheter into epidural space (1 case) and retroduodenal perforation (1 case). In the OAI-group, three patients were excluded from the study: due to massive bleeding (1 case), retroduodenal perforation (1 case), and retention of the Dormia basket (1 case), which required surgical interventions.

As a result, the results of treatment of 195 patients (98 patients of the TEA group and 97 patients of the NAI group) were analyzed.

The studied indicators (demographic data, the nature of the disease, the results of laboratory or instrumental research, outcomes, etc.) were entered into the database within 10 days after the intervention.

Statistical analysis of the data was performed using nonparametric tests (OR and Fisher's exact test). The groups were divided into subgroups taking into account age, sex, nature of the disease, severity of concomitant pathology, types of ETI. For each of the subgroups, the odds ratio (OR) was calculated with a 95% confidence interval (95% CI). A statistically significant difference between the study groups (subgroups) was considered $p \leq 0.05$ (an indicator of statistically significant differences) or when the 95% confidence interval (CI) did not include 1. Statistical processing of the data was carried out using a set of statistical programs Statistica 10.0 (StatSoft Inc., USA).

RESULTS AND DISCUSSION

The demographic data of the patients are presented in Table 1. In the TEA-group, the average age of the patients was 61.4 ± 1.3 years, in the OAI-group — 60.9 ± 1.2 years. There were no statistically significant differences in the number of women and patients of young age (under 60 years) and more advanced age (over 60 years) (OR 0.94 [95% CI, 0.53–1.66]) and (OR 1.06 [95% CI, 0.60–1.88], respectively).

The study groups did not differ in other indicators either. In the TEA group and the OAI group, there was a commensurate number of patients with tumors of the hepatopancreatobiliary zone (33.7% [33/98] versus 33.0% [32/97] cases, OR 1.03) and with jaundice (38.8% [38/98] versus 38.1 % [37/97] cases, OR 1.03); with choledocholithiasis (36.7% [36/98] versus 38.1% [37/97] cases, OR 0.94) and with sphincter of Oddi dysfunction (SOD) (12.2% [12/98] versus 11.3% [11/97] observations, OR 1.09).

Concomitant diseases were detected in 58.2% (57/98) of patients in the TEA group and in 61.9% (60/97) of patients in the OAI group (OR 0.85 [95% CI, 0.48–1.53]). The study groups also did not differ in the number of patients with severe comorbidity (ASA IV) (OR 1.13 [95% CI, 0.41–3.08]). The majority of patients in this category were diagnosed with diseases of the cardiovascular system (84.2% [48/57] of patients with the TEA group and 85.0% [51/60] of patients with the OAI group).

The study groups also did not differ on other variables. Based on the above, the study groups represented patients with similar baseline parameters, and this could not affect the reliability of the results.

Depending on the nature of the disease, various types of endoscopic transpapillary interventions were used. The study groups did not differ in this indicator either. In the TEA group and the OAI group, endoscopic papillosphincterotomy was equally often used (in 82.7% versus 81.4% of cases (OR 1.09 [95% CI, 0.52–2.27])) and balloon dilation (in 18.4% versus 20.6% of cases (OR 0.87 [95% CI, 0.42–1.77])), biliary-stone extraction (in 51% versus 53.6% cases (OR 0.90 [95% CI, 0.51–1.59])) and lithotripsy (in 9.2% versus 10.3% of cases (OR 0.88 [95% CI, 0.34–2.29])), installation of biliary stent (31.6% versus 28.9% of cases (OR 1.14 [95% CI, 0.39–3.32])) and installation of pancreatic stent (19.4% versus 22.7% of cases (OR 0.82 [95% CI, 0.41–1.65])).

During this study, patients in the study groups were diagnosed with 15 (7.7% [15/195]) cases of PEP development. In 80.0% (12/15) of observations, this complication was registered in patients of the OAI-group (Table 2). The incidence of PEP in the TEA group was 3.1% (3/98), and in the OAI group — 12.4% (12/97) of observations, which is a statistically significant difference between the study groups (p = 0.0135).

The vast majority of cases of PEP in patients of the TEA group and OAI group were mild (66.7% [2/3] and 58.3% [7/12] observations, respectively) and their clinical manifestations could be stopped within 3 days. One of three patients (33.3%) of the TEA group and 4 of 12 (33.3%) patients of the NAI-group needed to continue anti-pancreatic therapy for up to 7 days. Taking into account the clinical picture, the data of laboratory and instrumental studies, in the NAI-group, pancreatonecrosis was verified in 1 (1.0%) patient. Symptoms of pancreatic necrosis in this patient developed rapidly and were characterized by total damage to the pancreas, complicated by the development of multiple organ failure, which led to death.

The incidence of post-ERCP pancreatitis in study subgroups different in gender, age, disease nature, severity of concomitant pathology and types of intervention is shown in Table 3.

A statistically significant decrease in the incidence of PEP with the use of TEA was found in patients

Table 1. Selected subject and procedural characteristics of patients

Variable	Total, n (%)		OR
	TEA group (N=98)	OAI group (N=97)	(95% CI)
Age			
18-40 y	9 (9.2)	8 (8.2)	1.13 (0.41-3.08)
41-60 y	38 (38.8)	40 (41.2)	0.90 (0.51-1.61)
61-80 y	39 (39.8)	36 (37.1)	1.12 (0.62-2.00)
>80 y	12 (12.2)	13 (13.5)	0.90 (0.39-2.11)
Gender			
Woman	59 (60.2)	61 (62.9)	0.89 (0.50-1.60)
Context			
Jaundice	38 (38.8)	37 (38.1)	1.03 (0.57-1.84)
Common bile duct stones	36 (36.7)	37 (38.1)	0.94 (0.52-1.69)
SOD	12 (12.2)	11 (11.3)	1.09 (0.45-2.63)
Common bile duct stones and SOD	14 (14.3)	15 (15.5)	0.91 (0.41-2.02)
Tumor	33 (33.7)	32 (33.0)	1.03 (0.56-1.88)
Calculous pancreatitis	3 (3.1)	2 (2.1)	1.50 (0.24-9.37)
ASA grade			
IV	9 (9.2)	8 (8.2)	1.13 (0.41-3.08)
III	21 (21.4)	22 (22.7)	0.93 (0.47-1.84)
I and II	68 (69.4)	67 (69.1)	1.01 (0.55-1.88)
Procedural			
Biliary sphincterotomy	81 (82.7)	79 (81.4)	1.09 (0.52-2.27)
Balloon dilation	18 (18.4)	20 (20.6)	0.87 (0.42-1.77)
Biliary-stone extraction	50 (51.0)	52 (53.6)	0.90 (0.51-1.59)
Installation of biliary stent	31 (31.6)	28 (28.9)	1.14 (0.61-2.12)
Lithotripsy	9 (9.2)	10 (10.3)	0.88 (0.34-2.29)
Installation of pancreatic stent	19 (19.4)	22 (22.7)	0.82 (0.41-1.65)
Naso-biliary drainage	8 (8.2)	7 (7.2)	1.14 (0.39-3.32)

Note. *P < 0.05, statistically significant; ASA — American Society of Anaesthesiologists; SOD — sphincter of Oddi dysfunction

Table 2. The incidence of post-ERCP pancreatitis in patients of the study groups

Post-ERCP pancreatitis	TEA group (N=98)	OAI group (N=97)	P, Fisher
Mild, n(%)	2 (2.1)	7 (7.2)	0.0823
Moderate, n(%)	1 (1.0)	4 (4.2)	0.1811
Severe, n(%)	0 (0.0)	1 (1.0)	0.4974
Total, n(%)	3 (3.1)	12 (12.4)	0.0135*

under 60 years of age (OR 0.18 [95% CI, 0.04–0.93]) and with the use of endoscopic papillosphincterotomy (OR 0.17 [95% CI, 0.04–0.85]).

A significant (but statistically insignificant) decrease in the incidence of PEP with the use of TEA was found in patients of all study subgroups: in women

(OR 0.31 [95% CI, 0.08–1.24]), in patients with jaundice (OR 0.22 [95% CI, 0.02–2.20]) and without it (OR 0.22 [95% CI, 0.04–1.14]), in patients with choledocholithiasis and SOD (OR 0.21 [95% CI, 0.02–2.29]) and in patients with isolated choledocholithiasis (OR 0.24 [95% CI, 0.02–2.32]), after balloon

Table 3. *The incidence of post-ERCP pancreatitis in patients of the study subgroups*

Variable	Post-ERCP pancreatitis n (%)		OR (95% CI)
	TEA group (N=98)	OAI group (N=97)	
Age			
18-40 y	1/9 (11.1)	2/8 (25.0)	0.38 (0.03-5.46)
41-60 y	1/38 (2.6)	6/40 (15.0)	0.15 (0.02-1.40)
61-80 y	1/39 (2.6)	3/36 (8.3)	0.29 (0.03-3.06)
>80 y	0/12 (0.0)	1/13 (7.7)	---
Gender			
Woman	3/59 (5.1)	9/61 (14.8)	0.31 (0.08-1.24)
Men	0/39 (0.0)	3/36 (8.3)	---
Context			
Jaundice	1/38 (2.6)	4/37 (10.8)	0.22 (0.02-2.20)
Common bile duct stones	1/36 (2.8)	4/37 (10.8)	0.24 (0.02-2.32)
SOD	0/12 (0.0)	1/11 (9.1)	---
Common bile duct stones and SOD	1/14 (7.1)	4/15 (26.7)	0.21 (0.02-2.29)
Tumor	1/33 (3.0)	3/32 (9.4)	0.30 (0.03-3.22)
Calculous pancreatitis	0/3 (0.0)	0/2 (0.0)	---
ASA grade			
IV	0/9 (0.0)	1/8 (12.5)	---
III	1/21 (4.8)	3/22 (13.6)	0.30 (0.03-3.31)
I and II	2/68 (2.9)	8/67 (11.9)	0.22 (0.04-1.13)
Procedural			
Biliary sphincterotomy	2/81 (2.5)	10/79 (12.7)	0.17 (0.04-0.85)*
Balloon dilation	1/18 (5.6)	5/20 (25.0)	0.18 (0.02-1.77)
Biliary-stone extraction	2/50 (4.0)	8/52 (15.4)	0.23 (0.04-1.18)
Installation of biliary stent	1/31 (3.2)	4/28 (14.3)	0.20 (0.02-2.00)
Lithotripsy	1/9 (11.1)	3/10 (30.0)	0.29 (0.02-3.67)
Installation of pancreatic stent	0/19 (0.0)	2/22 (9.1)	---
Naso-biliary drainage	1/8 (12.5)	2/7 (28.6)	0.36 (0.02-5.40)
Total, n(%)	3/98 (3.1)	12/97 (12.4)	0.22 (0.06-0.83)*

Table 4. *Frequency of post-ERCP pancreatitis in high-risk patients*

Post-ERCP pancreatitis	High risk patients		P, Fisher
	TEA group (N=46)	OAI group (N=43)	
Mild, n(%)	1 (2.2)	6 (14.0)	0.0454*
Moderate, n(%)	1 (2.2)	3 (7.0)	0.2830
Severe, n(%)	0 (0.0)	1 (2.3)	0.4831
Total, n(%)	2 (4.4)	10 (23.3)	0.0095*

dilatation (OR 0.18 [95% CI, 0.02–1.77]), biliary-stone extraction (OR 0.23 [95% CI, 0.04–1.18]) and naso-biliary drainage (OR 0.36 [95% CI, 0.02–5.40]), etc.

In some subgroups, patients from the TEA group did not have a single case of post-ERCP pancreatitis, namely, in patients over 80 years of age, in men, in patients with SOD, with calculous pancreatitis, with severe concomitant pathology (ASA IV), after installation of pancreatic stent. There were no lethal outcomes in patients of the TEA group.

More often, the early postoperative period was accompanied by the development of AKI in women (in 10.0% [12/120] cases), in young (up to 60 years old) patients (in 10.5% [10/95] cases), and in patients with choledocholithiasis and SOD (in 17.2% [5/29] observations). According to our data, these factors increased the risk of post-ERCP pancreatitis, and the subjects, who combined two or more risk factors, were attributed to patients with a high risk of PEP [1]. In the TEA group, 46.9% (46/98) were identified, and in the OAI group — 44.3% (43/97) of patients in this category. Table 4 presents data on the incidence of post-ERCP pancreatitis in patients at high risk of developing this complication.

As shown in the table, when TEA was used in patients with a high risk of PEP, its incidence decreased from 23.3% (10/43) to 4.4% (2/46) observations (p = 0.0095).

In patients with a low risk of developing this complication, the use of both TEA and indomethacin suppositories, as methods of preventing PEP, has shown commensurate efficacy. There was no statistically significant difference in these study subgroups (3.7% (2/54) observations in the NAI subgroup versus 1.9% (1/52) cases in the TEA subgroup (p = 0.5143)).

Throughout the entire period of the use of therapeutic ETI we havecontinued the search for methods of preventing the development of PEP. A lot of studies were carried out to study the preventive effect of the use of various groups of medicines (nitrates, sandostatin, heparins, etc.) [4, 6, 7, 11]. For this purpose, various endoscopic tactics of endoscopic interventions were proposed for use [1, 9, 10]. But despite this, development of post-ERCP pancreatitis has remained the main problem of therapeutic ETI.

As a result of our study, reliable data were obtained on the effectiveness of of TEA for preventing the development of PEP in ETI. A decrease in the incidence of post-ERCP pancreatitis from 12.4% to 3.1% was shown. In the TEA group, PEP was mild to moderate in all cases. The use of TEA helps prevent the development of pancreonecrosis and poor outcomes in patients, which significantly increases the safety of ETI in patients with a high risk of PEP and severe comorbidity. An important fact is that the use of TEA, as noted by endoscopists, creates more comfortable conditions for their work.

All patients were inpatient until the end of the study, so there was no data loss. The indicators were entered into the database in real time.

Of course, this method of prevention has its drawbacks. We refer to the main disadvantages: the need to involve a doctor who knows the methodology for conducting TEA; the invasiveness of the method (despite its safety); restriction in use in patients with coagulopathies (for example, in patients with hepatic insufficiency); the possibility of using only in hospitalized patients.

Of course, not all patients with therapeutic ETI need to use TEA. Obviously, in patients with a low risk of developing PEP, it seems sufficient to use a less invasive technique — indomethacin suppositories.

CONCLUSION

— The use of TEA is an effective and justified method of prevention in patients at high risk of developing PEP;

— In patients with a low risk of PEP, the use of TEA is inappropriate due to the invasiveness of the method.

In conclusion, we would like to note that this study does not question the effectiveness of other prevention methods recommended by different authors, but only complements them. Anyway, an individual approach to each patient is required.

Conflict of interests

The authors state that they have no conflict of interests.

Contributors

MIT and VVM collected, analysed, and interpreted data and made the figures. ASP did the literature review and collected data. AVE and YuIV collected data and made the figures. MIT and VVM interpreted and analyzed the data. MIT, ASP, AVE, YuIV and VVM prepared the manuscript for submission.

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