Gastrointestinal Tract

ORIGINAL ARTICLE

Prevention of severe post-ERCP pancreatitis? It is possible.

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ABSTRACT

Background and Objectives: The main issue of post-endoscopy pancreatitis (PEP) prevention remains an urgent and still an un-solved problem. Despite the relatively low incidence of severe pancreatitis development, treatment costs and mortality rates remain unreasonably high. The purpose of this article is to evaluate the author's technique for preventing severe PEP progression based on their personal experience. **Methods**: The study was conducted in a double-centered randomized setting in 836 patients with pancreatobiliary pathology who underwent endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic papillosphincterotomy (EPST) from 2016 to 2023. All patients were divided into 4 groups. Group 1 (341 patients) received conventional therapy consisting of medications and the use of a guidewire. Group 2 (100 patients) received a submucosal 10 ml saline injection postbulbar blockade (PBB) ("fake") in addition to standard premedication. Standard premedication and one "true" PBB with lidocaine or procaine were given to Group 3 (252 patients) upon the completion of the interventions. Group 4 consisted of 143 patients who were given standard premedication and a "true" double PBB (DPBB)—before and after the manipulation itself. **Results**: The evaluation of PBB's effectiveness was improved through the development of the DPBB technique. DPBB's effectiveness in PEP prophylaxis was demonstrated through the absence of severe PEP cases. The benefits of PBB and DPBB were not only rapid pain relief, but also prevention of post-papillotomy bleeding. Regardless of the method used for PEP prophylaxis, hyperamylasemia regression was longer with the use of plastic stents. The average admission period for patients after DPBB was 11.3 ± 1.2 days, which was significantly shorter than in other groups. **Conclusion**: DPBB was proven to be the most straightforward, simple, and effective technique for severe PEP prophylaxis in comparison with PBB and conventional methods.

Key words: hyperamylasemia, postbulbar blockade, post-endoscopy pancreatitis, pancreatic stent, biliary stent

INTRODUCTION

In the past few decades, the safety of endoscopic retrograde cholangiopancreatography (ERCP) has significantly improved due to the identification of risk factors for post-endoscopy pancreatitis (PEP) development and ways to prevent it. However, the incidence of PEP, especially severe PEP, has remained constant over the years.[1,2] PEP is fatal in 0.2% (0.1%–0.5%) and results in an annual cost of several hundred million dollars.[1,3,4] Even though there are various classes of medications, biodegradable stents, and combinations of techniques for PEP prophylaxis, complications following ERCP remain a dire issue.[2,5] Finding new, affordable, simple and effective methods of preventing PEP, particularly severe PEP, is now a

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priority for medical communities.[6,7] The aim of our study is to compare the efficacy of two author's PEP prevention techniques and also to demonstrate the capacity of simple techniques to avoid severe PEP progression.

MATERIAL AND METHODS

A prospective, two-center, randomized study included 836 patients with pancreatobiliary pathology who underwent ERCP and EPST in the Department of Liver Surgery and General Surgery between 2016 and 2023. There were 251 males (30%) and 585 females (70%) aged 18 to 92, with a mean age of 62.7 ± 7.4 years. The study was performed in compliance with the requirements of the Declaration of Helsinki adopted by the XVII World Health Assembly in 1964 and its subsequent revisions. The study protocol was approved by the local independent ethical committee. All patients signed informed consent prior participating in the study, and were divided into four groups according to the method of PEP prevention.

The first group included 341 patients. All patients in this group received standard medications (atropine sulfate 0.1%1 mL, diphenhydramine1% 1 mL, octreotide 0.01% 1 mL, diclofenac 2.5% 3 mL, nitrosorbide 10 mg sublingually) with no endoscopic submucosal injections.

Group 2 (100 patients) received a submucosal 10 mL normal saline injection "fake" postbulbar blockade (PBB) in addition to standard premedication. Standard premedication and one "true" PBB with lidocaine 2% 10 ml or procaine 0.5% 10 mL were given to Group 3 (252 patients) upon the completion of the interventions (Patent RU No. 23244803, 20. 05.05.2008). Group 4 consisted of 143 patients who were given standard premedication and a "true" DPBB = 2PBB—before and after the manipulation itself (Patent RU No. 2779221, 05.09.2022). The technique of performing DPBB is depicted in Figure 1 and Figure 2. The groups were comparable in terms of sex, age, disease structure and nature of intervention. Clinical manifestations of PEP and serum amylase level were monitored every 12 hours until normalization of the parameters.

Entry criteria

(1) Patients with a complicated form of gallstone disease—acute cholecystitis, cholangitis, cholangiogenic hepatitis, vesico-digestive fistulas, bilio-biliary fistulas (Mirizzi syndrome), cicatricial biliary strictures;

(2) Patients with choledocholithiasis and major duodenal papilla pathology (Sphincter of Oddi Dysfunction = SOD, stenosis of the major duodenal papilla, papillothiasis), regard less of obstructive jaundice presence.

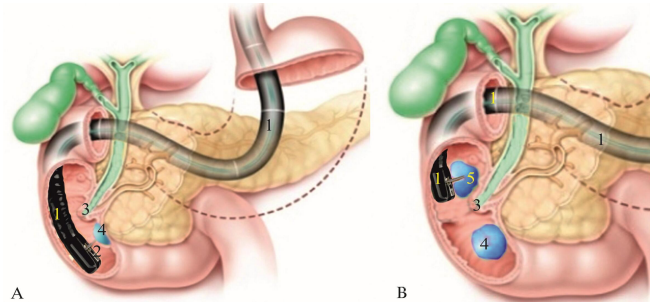

Figure 1. Scheme of DPBB execution. **A**. Creation of the first (distal) submucosal depot. **B**. creation of the second (final) submucosal depot. 1: endoscope; 2: injector; 3: papilla; 4: first submucosal depot; 5: second submucosal depot.

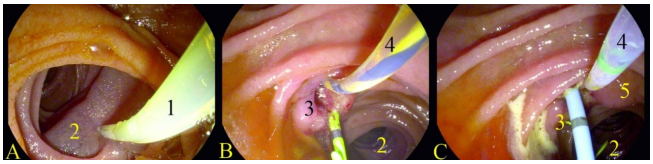

Figure 2. Use of DPPB in practice. **A**. Creation of the first (distal) submucosal depot. **B**. Transpapillary manipulations. **C**. Creation of the second (final) submucosal depot at the edge of papillotomy. 1: injector; 2: submucosal depot: 3: papilla area; 4: catheter; 5: second submucosal depot.

Exclusion criteria

(1) Surgical jaundice of tumorous origin (liver, duodenum, papilla, bile ducts or gallbladder);

(2) Acute pancreatitis and/or necrotizing pancreatitis on admission or at the time of endoscopic intervention;

(3) Patient's refusal to participate in the study.

The characteristic of patients with respect to gender and age is presented in Table 1.

Statistical data processing was performed using Statistica 10.1 application (Stat-Soft, Russia). In our study, we used Mann-Whitney criteria for two independent group comparison and Kruskal-Wallace criteria for k-independent groups ($k > 2$) of ordinal signs comparison. We also applied Chi-square (χ^2) and z-criterion for comparison of independent groups of qualitative signs. The normality of quantitative signs was checked by calculating the characteristics of skewness and kurtosis of the distribution. In case of normal distribution, the mean (M) with standard deviation were used to describe the signs. In the absence of normality—median and quartiles. The null hypothesis (H0) assumes that differences in the compared groups are not significant. Differences were considered significant (H0 was rejected) at the significance level of difference $P < 0.05$.

Table 1: Characteristic of patients by gender and age

Age (years)	Group 1 (standard medication)				Group 2 (false PBB)				Group 3 (PBB)				Group 4 (DPBB)			
	Men		Women		Men		Women		Men		Women		Men		Women	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
⩽ 20	0	0	0	0	0	0	0	0	0	0	1	0.6	0	0	0	0
21–30	4	4.3	0	0	0	0	8	11	1	1.2	6	3.5	4	9	4	4
31–40	5	5.4	1	4	1	4	2	3	6	7.3	15	8.8	4	9	6	6
41–50	8	8.6	4	14	4	14	12	16	8	9.8	15	8.8	4	9	6	6
51–60	17	18.3	5	18	5	18	13	18	12	14.6	26	15.3	2	5	8	8
61–70	24	25.8	10	36	10	36	20	28	25	30.5	47	27.7	15	35	30	30
71–80	27	29	6	21	6	21	10	14	19	23.2	41	24	8	19	32	32
⩾ 80	8	8.6	2	7	2	7	7	10	11	13.4	19	11.3	6	14	14	14
Total	93	100	28	100	28	100	72	100	82	100	170	100	43	100	100	100
In group		27.3		32.5		32.5		67.5		32.5		67.5		26.4		73.6

PEP: post-endoscopy pancreatitis; DPBB: double PBB.

RESULTS

The efficacy of PEP prophylaxis methods had revealed the advantages of DPBB (Figure 3). Severe PEP was not detected in the Group 4with DPBB (χ^2 = 8.23, P =0.0041).

However, the incidence of mild PEP was significantly lower PBB against DPBB (χ^2 = 11.35 P = 0.0008), but similar comparing to standard PEP prophylaxis (χ^2 = 1.07, P = 0.3007) (Figure 4). Intravenous sedation or general anesthesia were used in 275 (32.9%) of cases.

The benefit of PBB and DPBB was not only rapid pain relief "on the needle", but also hemorrhage prophylaxis. Submucosal injection with local anesthetic in the area of papillotomy (similar to infiltration hemostasis) protected all the patients from development of post manipulation bleeding.

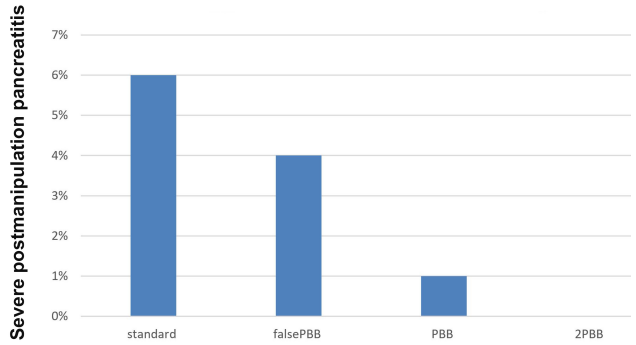

Figure 3. Incidence of severe post-endoscopy pancreatitis among groups.

However, in those cases when reactive hyperamylasemia

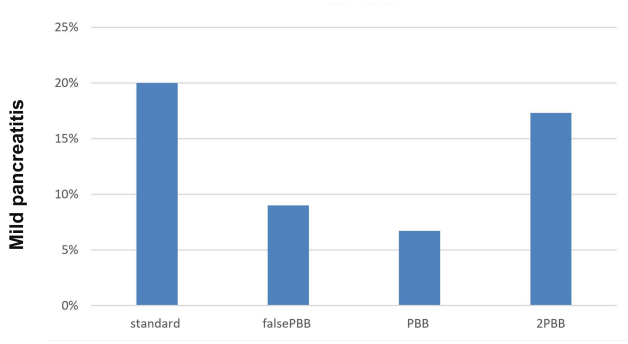

Figure 4. Incidence of mild post-endoscopy pancreatitis among groups.

was detected, it appeared that PBB caused more frequent asymptomatic rise of amylase levels ($\chi^2 = 6.81$, $P = 0.0091$). On the other hand, such differences weren't detected between groups with standard prophylaxis and DPBB ($\chi^2 = 0.05$, $P = 0.8212$) (Figure 5).

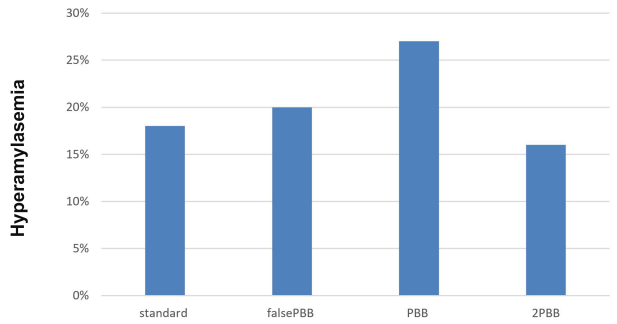

Figure 5. Incidence of reactive hyperamylasemia among groups.

This may be connected with the fact that some procedures were done without any general anesthesia. In those cases when pain emerged during endoscopy, PBB allowed us to control it quickly and effectively. But we should not forget that pain is rather a sign of pancreatic damage and subsequent predictor of amylase level spike.

For additional evaluation, we allocated a subgroup of 197 patients, where we used biliary and/or pancreatic duct stenting for PEP prophylaxis. The frequency of stenting differed between the groups ($\chi^2 = 9.04$, $P = 0.0026$) (Figure 6). Biliary stenting was used most of the times in all the groups, even though double stenting was used least frequently. In DPBB group, stenting was used significantly less often ($\chi^2 = 23.22$, $P = 0.0000$) (Figure 7).

According to our data, the use of stents resulted in a longer regression period of hyperamylasemia regardless

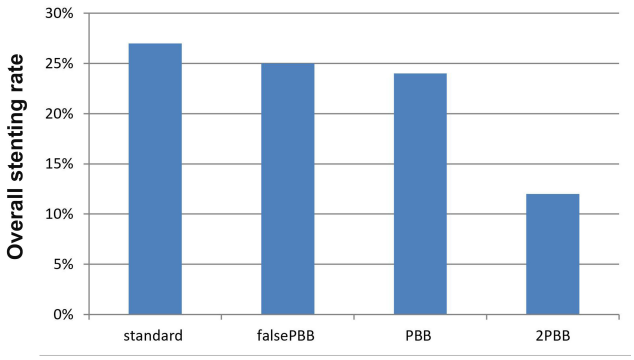

Figure 6. Total frequency of stenting among groups.

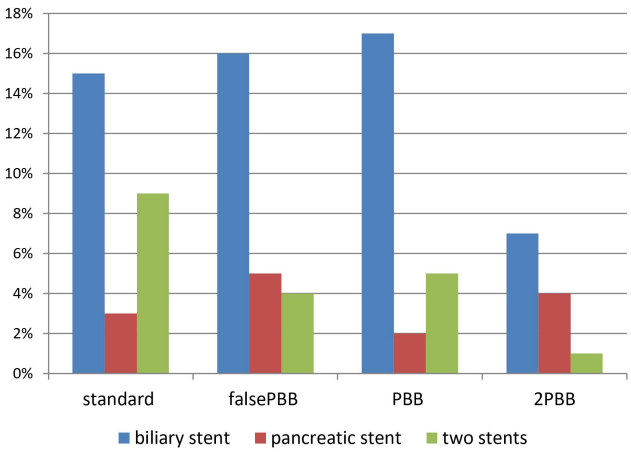

Figure 7. Rate of different stenting in each group.

of the method of PEP prophylaxis: 3.2 ± 1.2 days without stenting, 5.8 ± 1.6 days with stenting ($\chi^2 = 76.26$, $P = 0.0000$) (Figure 8).

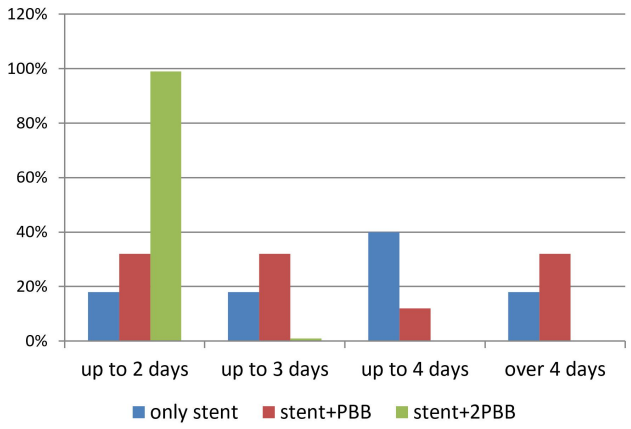

Figure 8. Duration of regression of hyperamylasemia using stents.

Methods of PEP prophylaxis were cross-coupled with a

type of EPST. While atypical EPST was the most common cause of PEP in the group with standard PEP prophylaxis (χ^2 = 8.10, P = 0.0044), this association was absent in the groups with PBB (χ^2 =0.09, P = 0.7674) and DPBB (χ^2 = 0.32, P = 0.5698) (Figure 9).

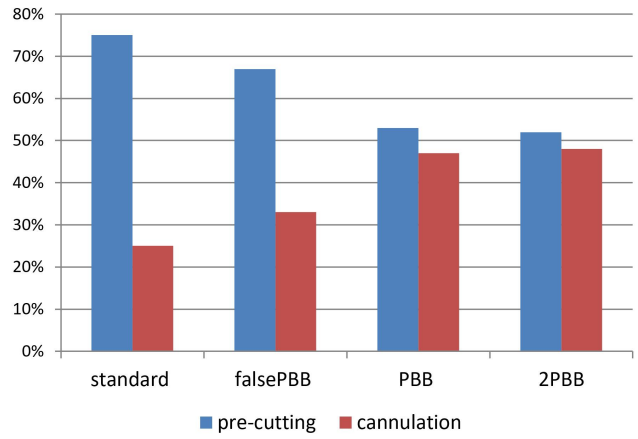

Figure 9. Incidence of post-endoscopy pancreatitis with regret to the type of endoscopic papillosphincterotomy.

The length of hospital stay showed significant differences between the groups (χ^2 = 36.46, P = 0.0000). The mean length of hospital stay for DPBB was 11.3 ± 1.2 days and was remarkably shorter comparing to other groups.

DISCUSSION

Prevention of PEP, especially with known risk factors, remains a complicated challenge for physicians everywhere.[8] Medical therapy is known to be effective in reducing the incidence of mild PEP.[7] However, drug prophylaxis of PEP, even during ERCP, is not a safeguard of success. It motivates surgeons to look up for effective preventive methods further.[2,8] Acute pancreatitis after ERCP most commonly is mild one. Less often it appears to be moderate, but in about 10% of cases (about 0.4%–0.6% of ERCPs), it is severe and potentially fatal. Furthermore, asymptomatic hyperamylasemia occurs in 35%–70% of patients undergoing ERCP.

The wide range of published incidence of acute pancreatitis (from 2.7% to 37%) can be explained and widely depends on the criteria used for diagnostic assessment, type and duration of the follow-up.[2–4,9] PEP prophylaxis is particularly relevant in case of intact papilla with no signs of biliary hypertension.[10–12]

In patients with high-risk of PEP development, duct stenting allows us to reduce the proportion of severe PEP due to a shift towards mild PEP[2,10] in the statistics of the complications.

However, in addition to the high price of stents, our data showed that stenting itself is a risk factor of a longer hyperamylasemia in combination with PBB (Figure 8). International literature also demonstrates that the use of stents is a risk factor for PEP progression.[8,13]

Also, stenting was used significantly less frequent in the DPBB group, and the incidence of severe PEP was minimal. Recommendations for massive infusion of Ringer's lactate are also questionable in terms of time, cost, and expected outcome.[2,8] As we demonstrated, both PBB and DPBB techniques showed a direct and pronounced effect in reduction of the PEP response. However, DPBB, in our opinion, was more effective and relevant in preventing severe PEP, the speed of hyperamylasemia regression, and shortening in-hospital period. An additional advantage of PBB and DPBB is the prevention of bleeding. The proposed PEP prophylaxis technique, was used independently of PEP risk factors, and was more effective than standard PEP prophylaxis techniques.

No doubt that PEP prophylaxis is a compound process, including cannulation technique, access choose and intervention time, type of anesthesia, drug combinations, *etc.*[2,7,14,15] Despite the wide range of guidelines for the prevention of ERCP-connected complications, for different reasons many doctors do not always use them. Nevertheless, our results indicate high efficacy of a new method of PEP prophylaxis—DPBB, which can be used routinely and in combination with other techniques in all the cases of known risk factors of PEP.[16,17]

There is no universal and ideal way to prevent pancreatic reaction to endoscopic intervention. However, DPBB is the most effective way to prevent severe PEP development comparing to PBB and standard PEP prophylaxis approaches. DPBB can be used as a routine preventive technique for PMP in all categories of patients.

DECLARATIONS

Source of Funding
The study received no external funding.

Conflicts of interest
The authors declare no conflict of interest.

Data sharing statement
No additional data is available.

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