Small caliber pancreatic stents in the management of acute biliary pancreatitis and the prevention of post-ERCP pancreatitis

Doctoral (PhD) Thesis

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1. LIST OF PUBLICATIONS

1.1. First author papers related to this thesis (n=7, cumulative impact factor: 16.956, cumulative citation: 60)

I. **Dubravcsik Z**, Gyökeres T, Novák P, Budai A, Mohácsi S, Velkei T, Madácsy L. Az endoszkópos retrográd cholangiopancreatographia szövődményei. [Complications of endoscopic retrograde cholangiopancreatography] Orv Hetil. 2022; 163: 911-919. **(Q3, H index: 21, IF: 0.41, citated: 0)**

II. **Dubravcsik Z**, Hritz I, Szepes A, Madácsy L. Risk factors of post-ERCP pancreatitis in high-risk patients despite prevention with prophylactic pancreatic stents. Scand J Gastroenterol. 2020; 55: 95-99. **(Q2, H index: 105, IF: 2.218, citated: 3)**

III. **Dubravcsik Z**, Hritz I, Szepes A, Madácsy L. Profilaktikus sztentek alkalmazása az endoszkópos retrográd cholangiopancreatographiát követő pancreatitis megelőzésében. [Prophylactic stents in the prevention of pancreatitis following endoscopic retrograde cholangiopancreatography]. Orv Hetil. 2021; 162: 31-38. [Hungarian] **(Q3, H index: 21, IF: 0.41, citated: 0)**

IV. **Dubravcsik Z**, Hritz I, Keczer B, Novák P, Lovász BD, Madácsy L. Network meta-analysis of prophylactic pancreatic stents and non-steroidal anti-inflammatory drugs in the prevention of moderate-to-severe post-ERCP pancreatitis. Pancreatology. 2021; 21: 704-713. **(Q1, H index: 74, IF: 3.996, citated: 1)**

V. **Dubravcsik Z**, Szepes A, Hritz I, Madácsy L. Small-caliber rescue pancreatic stenting for severe post-ERCP pancreatitis: a useful tool to pull the pancreas out of the fire. Endoscopy 2015; 47: 467–468. **(Q1, H index: 143, IF: 4.749, citated: 1)**

VI. **Dubravcsik Z**, Hritz I, Fejes R, Balogh G, Virányi Z, Hausinger P, Székely A, Szepes A, Madácsy L. Early ERCP and biliary sphincterotomy with or without small-caliber pancreatic stent insertion in patients with acute biliary pancreatitis: better overall outcome with adequate pancreatic drainage. Scand J Gastroenterol. 2012; 47: 729-736. **(Q2, IF: 2.423, citated: 30)**

VII. **Dubravcsik Z**, Madácsy L, Gyökeres T, Vincze Á, Szepes Z, Hegyi P, Hritz I, Szepes A. Hungarian Pancreatic Study Group. Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology. 2015; 15: 115-123. **(Q1, IF: 2.75, citated: 25)**

1.2. Non-first author papers related to this thesis (n=3)

I. Hritz I, **Dubravcsik Z**, Szepes A, Madácsy L. Does removal of prophylactic pancreatic stents induce acute pancreatitis? Gastrointest Endosc. 2011; 74: 1429–1430. (Q1, IF: 2.884, citated: 1)

II. Hritz I, Czakó L, **Dubravcsik Z**, Farkas G, Kelemen D, Lásztity N, Morvay Z, Oláh A, Pap Á, Párniczky A, Sahin-Tóth M, Szentkereszti Z, Szmola R, Szücs Á, Takács T, Tiszlavicz L, Hegyi P; Hungarian Pancreatic Study Group. Akut pancreatitis. A Magyar Hasnyálmirigy Munkacsoport bizonyítékon alapuló kezelési irányelvei. [Acute pancreatitis. Evidence based management guidelines of the Hungarian Panceatic Study Group]. Orv. Hetil., 2015; 156: 244–261. [Hungarian] (Q3, H index: 21, IF: 0.28, citated: 59)

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II. Czakó L, **Dubravcsik Z**, Gyökeres T et al. Az endoszkópos retrográd cholangiopancreatographia oktatásának hazai helyzete az Európai Emésztőszervi Endoszkópos Társaság (ESGE) oktatási irányelve tükrében. Central European Journal of Gastroenterology and Hepatology. 2022; 8: 2-10.

III. **Dubravcsik Z**, Gyökeres T, Hritz I, et al. Az endoszkópos leletezés standard nyelve. A nemzetközileg érvényes klasszifikációk gyűjteménye. Central European Journal of Gastroenterology and Hepatology. 2021; 7: 157-163.

IV. Gyökeres T, Bor R,….. **Dubravcsik Z**, et al. Quality expectations in endoscopy – Hungarian guideline [Az endoszkópia minőségi követelményei. Magyar szakmai irányelv.] Magy Seb. 2021; 74: 75-103. [Hungarian]

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VI. Gonczi L, Szanto K, ….. **Dubravcsik Z**, et al. Clinical efficacy, drug sustainability and serum drug levels in Crohn's disease patients treated with ustekinumab - A prospective, multicenter cohort from Hungary. Dig Liver Dis. 2021: S1590-8658(21)00377-7.

VII. Bor R, Szántó KJ, ….. **Dubravcsik Z**, et al, Hungarian GI Endoscopy COVID-19 Study Group. Effect of COVID-19 pandemic on workflows and infection prevention strategies of endoscopy units in Hungary: a cross-sectional survey. BMC Gastroenterol. 2021; 21: 98.

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IX. Lovász BD, Szalai M,….**Dubravcsik Z,** et al. Improved adenoma detection with linked color imaging technology compared to white-light colonoscopy. Scand J Gastroenterol. 2020; 55: 877-883.

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XV. Madácsy L, **Dubravcsik Z**, Szepes A. Postcholecystectomy syndrome: From pathophysiology to differential diagnosis - a critical review. Pancreat Disord Ther 2015; 5: 162.

XVI. **Dubravcsik Z**, Hritz I, Fejes R, et al. Endoscopic therapy of refractory post-papillotomy bleeding with electrocautery forceps coagulation method combined with prophylactic pancreatic stenting. Video Journal and Encyclopedia of GI Endoscopy 2014; 1: 628-631.

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2. INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas. Treatment costs of gastroenterological diseases are the highest in healthcare. It should be noted, that acute pancreatitis is the third most common cause of hospitalization. Gallstones and alcohol consumption are the two most common etiological factors comprising 2/3 of all cases, but there are other known causes, including endoscopic retrograde cholangiopancreatography (ERCP).

The average mortality of AP is 5%. In mild pancreatitis it is only 3%, but in severe (necrotizing) forms it is much higher, 17%, and in cases of infected necrosis it can reach 30%.

2.1. Diagnostic criteria of acute pancreatitis

AP has been defined (and classified) using the revised Atlanta Classification since 2013.

The diagnostic criteria follows the "two out of three" rule (2 of the following 3 should be present: 1 - abdominal pain characteristic of pancreatitis, 2 - elevation of serum amylase and/or lipase at least three times the upper limit of normal (ULN), 3 - abnormalities characteristic of AP detected on imaging).

2.2. Morhological types and complications of acute pancreatitis, phases of inflammation

Two AP types are defined **morphologically**. The first is interstitial edematous pancreatitis (enlargement of the pancreas, moderate stranding of the surrounding fat, minimal peripancreatic fluid). The vast majority of cases present in this form and recover in a few days. The other type is necrotizing pancreatitis (involves necrosis of the pancreas, or peripancreatic tissue, or both). It accounts for 5-10% of cases. The course of the disease is variable, the recovery is longer and the mortalitiy is higher.

Currently three forms of **complications** are defined, namely organ failure, local and systemic complications. Organ failure can occur in the cardiovascular, respiratory and renal organ systems, and can be transient (≤48 hours) or persistent (>48 hours). Local complications include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis. Systemic complications include recent onset organ failure, and progression of preexisting comorbidities (e.g. worsening of coronary artery or chronic pulmonary diseases).

There are two, partly overlapping inflammatory **phases**, and mortality has two peaks correspondingly. The early phase is usually detected in the first week, although it may extend into the second week. During this phase, activation of the cytokine cascade is present, which is

clinically characterized by systemic inflammatory response syndrome (SIRS), and may lead to persistent organ failure. The second, late phase lasts for weeks, sometimes months. By definition, it is characterised by the persistence of inflammatory signs or by local complications, therefore it is only seen in moderate to severe AP. In this case SIRS is followed by a compensatory anti-inflammatory response syndrome (CARS), which is responsible for the higher infectious complications during this phase.

3.3. Severity classification of acute pancreatitis and prognostic indices

Three **severity** forms, namely mild, moderate and severe AP is defined. It is mild, if there is no organ failure or local or systemic complications. It resolves in a few days without any complications, and mortality is extremely rare. It is moderate, if organ failure is transient or local or systemic complications occur. This form has a better prognosis than severe AP and may resolve spontaneously, but requires longer time, than mild cases. In severe cases, organ failure is persistent, and can involve only a single or multiple organs (multi-organ failure=MOF), with a markedly high mortality of 36-50%.

Various **prognostic indices** have been developed over the years. The accepted, international, consensus-based recommendation is the presence of SIRS and organ failure, but there have been a number of severity indices. It should be noted, that none of these is good enough to predict severity, as they generally have a medium sensitivity and low positive predictive value. In the past few years, artificial intelligence has also been used to estimate and predict severity, mortality, complications and disease progression.

3. PATHOPHYSIOLOGY OF ACUTE PANCREATITIS

The exocrine pancreas produces 2 liters of digestive enzyme- and bicarbonate rich ($HCO3^-$) fluid per day, which is crucial for normal digestion. The acinar cells produce the low volume but digestive enzyme-rich fluid, while the ductal cells produce the high volume and $HCO3^-$-rich fluid. The food coming from the stomach is acidic, which is neutralized by this alkaline, $HCO3^-$-rich fluid, and digestion of the food begins by activation of the digestive enzymes.

In exocrine pancreatic cells, intracellular Ca^{2+} levels play an important role. Its increase stimulates enzyme secretion in acinar cells, while fluid and electrolyte secretion in ductal cells. Abnormal, unregulated elevation of Ca^{2+} levels, on the other hand, leads to acute pancreatitis.

The various known etiological factors all trigger the disease through a sustained abnormal increase in intracellular Ca^{2+} levels, causing premature activation of trypsinogen in acinar cells and impaired fluid and $HCO3^-$ secretion in ductal cells. Other pathophysiological events also occur, such as mitochondrial failure, endoplasmic reticulum (ER) stress, abnormal unfolded protein response (UPR), or increased production of reactive oxygen species (ROS). These ultimately lead to acinar cell necrosis and local and systemic inflammatory responses.

As the disease can lead to serious health impairment or even death, and no specific medical treatment is available, better understanding of the underlying molecular mechanisms has been the subject of intensive research.

Using an American opossum model, it was demonstrated that ligation of the pancreatic duct without the presence of bile acids can induce necrotizing AP. Human studies have also demonstrated that transient obstruction of the pancreatic duct can lead to AP.

The pathophysiological processes that have been described so far have been established in animal models, mostly in rodents. It is known, that pancreatitis in rodents and humans differs, however, the mechanisms revealed in animal models have been demonstrated in ex vivo experiments in human pancreas cells.

3.1. Important pathophysiological molecular events

In response to alcohol, CCK or bile acids, Ca^{2+} is released from the endoplasmic reticulum (ER) of acinar cells via inositol-triphosphate receptors. The mechanoreceptor PIEZO1, which is activated by an increase in intraductal pressure in the Wirsung's duct, can also trigger the process. Reduced Ca^{2+} levels in the ER activate ORAI1 (Ca^{2+}-release activated Ca^{2+} channel protein 1), resulting in Ca^{2+} influx from the extracellular space into the ER and the cell. The increase in intracellular Ca^{2+} levels causes the MPTP (mitochondrial permeability transition pores) found in mitochondria to open, causing mitochondrial dysfunction by eliminating the membrane potential, which is essential for ATP production. The decreased ATP levels also impair the function of the ATP-dependent Ca^{2+} channels SERCA (sarcoplasmic reticulum Ca^{2+} channel) and PMCA (plasma membrane Ca^{2+} channel), that are both essential in maintaining the physiological Ca^{2+} homeostasis, resulting in Ca^{2+} accumulation. Pathological Ca^{2+} levels have cytotoxic consequences, such as premature trypsinogen activation, impaired autophagy, and activation of calcineurin and NF-κB (nuclear factor-κB), that lead to the production of proinflammatory cytokines. All of these steps cause acinar cell necrosis and an amplification of the inflammatory process.

Elevated intraductal pressure inhibits ductal cell secretion by activating 5-HT_3 receptors, leading to acidification. Intraductal acidification activates transient receptor potential vanilloid 1 (TRPV1) and leads to pancreatitis. The increased pressure can cause loosening of the tight junctions between acinar cells, thus the cells move away from each other, and enzymes released from the disintegrating cells can enter the intercellular spaces, exacerbating the self-digestion.

PIEZO1, calcineurin and TRPV1 mediated mechanisms are highly characteristic of both post-ERCP and biliary pancreatitis.

4. CLINICAL ASPECTS OF POST-ERCP AND ACUTE BILIARY PANCREATITIS

4.1. Post-ERCP pancreatitis (PEP)

ERCP is one of the well known etiological factors of AP, and PEP is one of the most frequent and potentially most severe complication of ERCP. Its incidence is 9.7%, and mortality rate is 0.7% in general, but in high-risk patients these indicators are 14.7% and 0.2% respectively.

The patomechanism is not fully understood, but several factors are thought to play a role in it. Mechanical stress on the Vater papilla and sometimes on the pancreatic duct (PD) during the cannulation maneuver, chemical and hydrostatic effects during contrast filling, thermal effects due to papillotomy (EST), enzymatic and even microbiological insults are also suspected. An important element is the increase in intraductal pressure in the PD.

4.1.1. Definition and severity classification of PEP

Diagnosis of PEP is defined by the Cotton consensus criteria as a new or worsened abdominal pain, with serum amylase or lipase levels at least three times the ULN at more than 24 hours after the ERCP, requiring hospital admission or a prolongation of a planned admission. These criteria classify PEP into 3 subgroups. Mild forms require hospitalization for 2-3 days, while PEP is moderate, when hospitalization lasts for 4-10 days, and severe when the patient is hospitalized for >10 days or develops complications, or requires intervention or surgery. It was the most commonly used and accepted classification system over the past 30 years, therefore we used it in our research.

4.1.2. Risk factors of PEP

A huge body of knowledge on the risk factors and preventive measures of PEP has accumulated. The risk factors based on the 2010 ESGE guideline are summarized in Table 1.

The patient is at high-risk of developing PEP if there is at least 1 definite or 2 likely risk factors present.

Table 1: Risk factors of post-ERCP pancreatitis

Risk factors	Odds Ratio	Risk factors	Odds Ratio
PATIENT-RELATED RISK FACTORS		**PROCEDURE-RELATED RISK FACTORS**	
Definite risk factors		***Definite risk factors***	
- suspected SOD	4.09	- precut sphincterotomy	2.71
- female gender	2.23	- pancreatic injection	2.2
- previous pancreatitis	2.46		
Likely risk factors		***Likely risk factors***	
- younger age	1.09-2.87	- >5 cannulation attempts	2.40 - 3.41
- non-dilated bile ducts	no data	- pancreatic EST	3.07
- abscence of CP	1.87	- papilla balloon dilation	4.51
- normal serum bilirubin	1.89	- failed CBD clearance	3.35

CBD=common bile duct, CP=chronic pancreatitis, EST=endoscopic sphincterotomy, SOD=sphincter of Oddi dysfunction

4.1.3. Prophylactic methods of PEP

Prophylactic measures range from adequate ERCP indication, through using low risk cannulation techniques, to active prophylaxis.

In active prophylaxis, the most important options are rectal non-steroidal anti-inflammatory drug (NASID) suppositories and PPS, although more recently high-volume hydration and sublingual nitrate have been incorporated into the recommendations. In the lack of contraindications, all patients should receive a 100 mg indomethacin or diclofenac NSAID suppository half an hour before or immediately after ERCP (the most recent recommendation suggests to use it before the examination). It reduces the risk of PEP to 60% compared with placebo (OR 0.60) and the number needed-to-treat (NNT) is 20. However, in high-risk patients, PPS can reduce the risk of PEP to 40%. It significantly reduces the risk of both mild-to-moderate and severe PEP (RR 0.45 and 0.26, respectively) and this effect applies to both the high-risk and unselected patient groups (RR 0.41 and 0.23, respectively), the NNT being 8.

4.2. Acute biliary pancreatitis (ABP)

The evidence of gallstones as etiological factors in AP was first described by Opie in 1901. According to his „common channel hypothesis" a gallstone, when impacted in the Vater papilla, occludes both the CBD and the PD, which then causes reflux of the bile into the

pancreas leading to early, intraductal activation of the pancreatic enzymes and AP. However, it has been proven since decades that gallstone impaction is mostly temporary.

PD obstruction, increased intrapancreatic duct pressure, PD disruption and acinar hyperstimulation all play an important role in the pathogenesis. On the other hand, individual vulnerability of the pancreas, individual difference of inflammatory responses, and edema or prolonged spasm of the pancreatic segment of the sphincter of Oddi can explain why ABP develops in some patients when a gallstone passes through the papilla, however, only a transient biliary colic and/or elevation of the liver function tests can be observed in others.

4.2.1. Role of ERCP in ABP

Introduction of ERCP into clinical practice, the development and improvement of its therapeutical methods opened up new horizons in minimal invasive treatment of pancreatobiliary diseases. The first ERCP procedures and Vater papilla cannulations were performed in the late 1960s, followed by the first papillotomies and the first biliary stenting in the 1970s.

The first period of ERCP usage in ABP ranges from the early 1980s to the early 2000s. Animal and human data showed, that the longer the biliary obstruction persists, the more likely AP becomes severe. When the obstruction persists beyond 48 hours, severe necrotizing course is detected in nearly 85% of patients.

The first 3 randomized controlled trials (RCT) demonstrated the superiority of early ERCP (within 72 hours) over conservative treatment in predicted severe ABP in reducing complications and hospital stay. Some of these studies were criticized on several reasons. In one study, AP severity was predicted with a controversial method, and patients with acute cholangitis were not excluded; on the other hand, the results of another one were only published in abstract form.

A German study investigated whether ERCP is still beneficial if there is no persistent biliary obstruction, therefore patients with jaundice were excluded. The endoscopic intervention did not result in fewer complications, in fact, the rate of respiratory failure was higher in the intervention group, so the study was stopped earlier. The study was criticized, as the number of enrolled patients/center was low, questioning the appropriate endoscopic practice. An Argentinian group investigated whether early ERCP is still beneficial in AP without acute cholangitis but with biliary obstruction. In terms of complications, there was no difference compared to conservative treatment.

Later on, meta-analyses arose around the millennium, but with conflicting results. An American group concluded that early ERCP, EST results in a better outcome compared to conservative treatment, however a meta-analysis by Petrov et al showed that in cases of ABP without associated acute cholangitis, regardless of AP severity, ERCP does not result in a better outcome.

Based on the recommendations by an international consensus in the early 2010s, ERCP is "clearly indicated" in ABP if co-existing acute cholangitis is present and "probably indicated" if common bile duct obstruction is present.

The debate is still ongoing. The Dutch Pancreatitis Study Group (DPSG) conducted intensive research on the subject. One of their RCTs showed that early ERCP had a better outcome compared to conservative treatment in severe ABP patients with cholestasis but no cholangitis. Another recently published multicenter RCT of the DPSG found no difference between early ERCP and systematic EST and conservative treatment in a similar patient population (severe ABP without cholangitis but with cholestasis) in terms of major complications and mortality. A recent meta-analysis showed, that early ERCP in ABP without cholangitis did not reduce either the complication rate or mortality compared to conservative treatment. Almost at the same time, an American study was published which, based on the data of more than 150,000 ABP patients without cholangitis, confirmed a significant reduction of mortality in the ERCP group.

The debate of ERCP in ABP can be explained by several factors, for example the lack of uniform definitions and criteria (eg. definition of biliary origin), or the early studies focused only on the predicted severity and not on CBD obstruction, or the timing of ERCP is not uniform, or complications of ERCP and their prevention methods were less known before, moreover, endoscopic intervention concentrates only on solving biliary obstruction, but does not affect PD obstruction and the increased intrapancreatic duct pressure.

5. RELEVANT RESULTS PRECEDING THE PRESENT RESEARCH TOPIC

5.1. Results described in PEP patients

We have previously shown that the literature recommends the usage of PPSs in high-risk patients for PEP prophylaxis. Madácsy et al reported a new way of using PPSs in high-risk patients. Sphincter of Oddi dyskinesis (SOD) patients, in whom biliary cannulation was difficult and the guidewire entered the PD several times, PPS implantation was performed first, instead of further forcing the standard cannulation methods, then a needle-knife fistulotomy

was done followed by the the biliary therapy. No PEP occured in the PPS group, but mild, moderate and even severe PEP cases were detected in the standard therapy group.

They published another pioneer concept too. In patients who underwent ERCP in whom PPS implantation was originally not applied, severe PEP was developed. During a second ERCP session a PPS was inserted into the PD of them 8-20 hours after the first procedure. Pancreatic pain was promptly reduced and no AP complications occurred, all PEP remained mild. The method was named "rescue ERCP". A few years later, American authors also described that this method is also beneficial in cases where a PPS is implanted during the original ERCP, but early dislodgment or blockage of PPS occured. PPS applied in the early phase of PEP reduces the intraductal pressure in the PD, and prevents the further progression of the pancreatitis.

5.2. Lowering the intrapancreatic duct pressure in ABP

Basic research shows, that although the patomechanizms of PEP and ABP are complex, the increase in intraductal pressure and the mechanisms mediated by PIEZO1, calcineurin and TRPV1 play an important role in both. We have seen that the application of PPS is very effective in the prevention, and also in cases of incipient PEP. Based on the similar pathogenetic steps, the idea may arise that PPS application can also be effective in ABP.

This was first reported by Hungarian authors. In ABP patients PPS implantation was only performed as a "bridging solution", because biliary cannulation was technically unsuccessful or contraindicated, and the biliary obstruction was resolved during a second session. There were significantly fewer complications, and mortality was also more favorable in this groups compared to the standard ERCP and EST patients.

5.3. Previous knowledge related to stent types

In cases of PEP prophylaxis and of ABP, a so-called small diameter (3-5 Fr) PPS is inserted into an intact Wirsung's duct. A meta-analysis showed, that the 5 Fr stent is better than the 3 Fr, as its insertion is technically easier and more successful. In a Japanese RCT the incidence of PEP was significantly lower using a short, 3 cm stent compared to 5 cm. Regarding the duration of stenting, only expert opinion is available. They should be in place for a minimum of 12-24 hours, but a maximum of 5-10 days.

Different stent designs are available among the small diameter, short stents, such as straight stents, with an external flange on the duodenal end, that can prevent migration into the PD, but on the inner end these stents either have a flange or not. The inner flange prevents early,

premature dislodgement. Stents without an inner flange is frequently used, as the PPS dislodges spontaneously and thus removal does not require another endoscopic procedure. In the case of certain stents, the outer flange is also omitted, the inner migration is prevented by the pigtail-like design of the outer end (this is the so-called Freeman type stent).

6. NULLHYPOTHESIS

It is well known, that the use of PPS significantly reduces the risk of PEP, but some patients still develop this complication, so we investigated how PPS affects some of the already known risk factors.

It is also known, that small-diameter, short PPSs without an inner flange are the most often used stents for PEP prophylaxis, however, there is no uniform recommendation regarding the stent types, so we examined stents of different designs in terms of efficacy and complications.

It is a well-known fact, that NSAID suppositories and PPSs are the most commonly used methods for active PEP prophylaxis, but we do not know if there is a difference between them in the prevention of moderate-severe PEP which is associated with severe health consequences, so we also examined this.

It is well known, that there are several common steps in the pathomechanisms of PEP and ABP. Considering that PPS promptly abolishes the elevated intraductal pressure, we investigated whether PPSs are effective not only for PEP but also for ABP.

7. AIMS

7.1. Aims in PEP-prevention

To analyze the data of our prospectively collected database of high-risk patients who underwent PPS implantation to prevent PEP, 1) firstly, targeting pancreatitis that develops despite PPS usage, 2) secondly, analysing stent types and stent-related complications, 3) thirdly, comparing the preventive effects of PPSs and NSAID suppositories in moderate-to-severe PEP.

7.2. Aims in ABP

To examine the PPS usage in ABP, 1) firstly, in a non-randomized study, where ERCP and biliary cannulation are difficult and procedure-related PEP risk factors are present, 2) secondly, later in a randomized fashion with developing a clinical study in this topic.

8. METHODS

8.1. Our research in PEP-prevention

8.1.1. PEP occurring despite using PPS, complications related to stents, and different stents types

A prospective database was initiated at the end of 2009 of high-risk patients with intact papillas without previous EST treated with PPS implantation for PEP prophylaxis. Predefined parameters were collected. PEP was defined and categorized according to the Cotton consensus criteria.

For PPS placement 5 Fr, 3–5cm stents were used. All stents were removed endoscopically in less than a week with polypectomy snare or foreign body forceps, unless dislodged spontaneously and the patient attended their follow up procedure. All patients were observed in hospital for at least overnight. They received similar treatment of nil by mouth for 8-12 hours and intravenous fluids (2000–3000 ml lactated Ringer's solution). NSAID suppositories were not used. Analgetics and spasmolytics were provided when required. Serum hemoglobin and amylase levels were tested at 6-8 hours after ERCP (the same evening) and the following morning (16–24 h post-procedure). Symptom free patients were discharged next morning, while PEP patients only after AP resolved and all complicated cases were followed up in 3 months. PEP was treated according to actual guidelines.

All stent related complications were registered, specifically paying attention to those described in the literature (early dislodgement, proximal migration, PD perforation, ductal and parenchymal changes, stent fragmentation in PD, AP induced by PPS removal). Data of the stented patients were compared to a historical cohort of similarly high-risk patients from 2000-2004, where PPSs were not used, as it was not part of the ERCP practice then.

Usual statistical methods (mean, standard deviation, Mann–Whitney U-test, independent samples t-test, Chi-square test, Fischer's exact test), data mining methods and random forest analysis were used. A $p<0,05$ considered as significant. Data mining and random forest analysis were used to examine which predictor had a greater impact on PEP. The analyses were carried out by an independent statistician with SPSS 19.0.0 (SPSS Inc., Chicago, IL) software.

8.1.2. Comparing PPSs and NSAID suppositories

In clinical practice, severe PEP can have a significant negative impact on the patient's health on the long term, therefore its prevention or shifting to a milder form is important. We compared the two most commonly used prophylactic methods in the form of a network meta-

analysis. Two reviewers independently searched the well known databases (PubMed, EMBASE, Cochrane Central Library) from initiation of the methods through 2nd January 2021. Reference lists of relevant studies, guidelines and meta-analyses were additionally searched for any other potential RCT. Only placebo controlled, rectal NSAID and PPS studies performed on adult population for prevention of PEP, published in full text were included. Placebo was the common comparator. The outcome measure was moderate to severe PEP defined according to the Cotton consensus criteria, as this was the most widely used, accepted, consensus based classification system over the past three decades, designed specifically for post-ERCP complications. The predefined protocol was registered in PROSPERO (CRD42020183641). The analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions. Search terms included: "NSAID", "non-steroidal anti-inflammatory drug", „indomethacin", "diclofenac", "prophylactic pancreatic stent", "preventive pancreatic stent", "PPS" and "post-ERCP pancreatitis". RCTs with imcomplete or missing data were excluded, unpublished data were not requested from authors.

Data were abstracted from eligible RCTs into a predefined database. The patient groups were classified as high-, low-, average-, or mixed-risk in the included studies. High-risk patients were analyzed separately, while low-, average- and mixed-risk patients were analyzed together classified as average-risk group.

Analysis was performed by a biostatistician with random effect model using Monte-Carlo methods, and interventions were ranked by their posterior probability via calculating the surface under cumulative ranking (SUCRA) curve values. Network estimates (pooled direct and indirect data) of each intervention compared to placebo and other interventions were presented in forest plots, summarized in a league table. All computations were performed using the R (V. 3.5.2) package gemtc (V. 0.8e2) along with the Markov Chain Monte Carlo engine JAGS (V. 3.4.0), package netmeta (V. 1.1e0), and STATA 16.0 (StataCorp LLC).

8.2. Our research in ABP

8.2.1. Non-randomized study

In 2009 a prospective, non-randomized trial was initiated in 2 large, Hungarian teaching hospitals. ABP patients in whom ERCP was indicated were enrolled.

The severity of AP was assessed using the Glasgow prognostic. All patients were hospitalized. All ERCP procedures was performed within 72 hours from the onset of pain. Indication for ERCP was ABP with concomitant clinical signs and laboratory and/or radiological signs of biliary obstruction and cholangitis. During the endoscopy procedure EST and CBD stone extraction was carried out for every patient, furthermore a PPS was inserted in the PD for patients with severe papillary edema due to impacted gallstone, repeated PD cannulation with a guidewire or contrast filling (>5), difficult biliary cannulation (>5 separate unsuccessful cannulation attempts during >10 minutes) or needle-knife precut papillotomy. All PPSs were removed during a gastroscopy within 10 days.

All patients received similar medical treatment irrespective of the study group, including aggressive fluid replacement, analgetics, spasmolytics and nasojejunal feeding when indicated. Antibiotic treatment was not started routinely for prophylaxis, only for therapeutic purposes. An abdominal contrast-enhanced CT scan was carried out on day 3–5 to detect any pancreatitis-related complications. Patients who responded very well were discharged at the end of the first week. All patients were scheduled for an out-patient follow-up within 4 weeks and monthly thereafter for a minimum of 3 months. A laparoscopic cholecystectomy was scheduled at 6 weeks after ABP.

At the final outcome-analysis the mortality rate within 90 days and the overall complication rate were exclusively analyzed, including intensive care unit transfer due to multi-organ dysfunction syndrome, septic shock or infected pancreatic necrosis, or pancreatic abscess, surgical interventions, large (>6 cm) pancreatic pseudocyst formation.

Statistical analysis was performed using the Mann–Whitney U test and the Fisher exact test with comparison of the individual groups.

8.2.2. Randomized study

Based on the results of our non-randomized study, we organized a multicenter, prospective, randomized, controlled, interventional trial in cooperation with the Hungarian Pancreatic Study Group (HPSG). The basics of the study was discussed and accepted on 7th October 2013 and all involved specialists signed a letter of intent to participate.

The aim of the trial is to compare the standard endoscopic treatment (EST and CBD stone extraction) with PPS implantation added to standard treatment in ABP cases where ERCP is indicated, irrespective of the predicted severity. The protocol was accepted by all participants and then submitted to the Hungarian National Ethical Committee, who approved it on 13th October 2014 (ETT-TUKEB ref.: 030174/2014/OTIG). The trial protocol was registered at the

International Standard Randomized Controlled Trial Number (ISRCTN) Register (trial ID: ISRCTN13517695), and published in an international peer-reviewed journal. The trial summary, protocol, ethical approval, letter of intent to join, patient informed consent and other documents were uploaded to the HPSG website (https://tm-centre.org/hu/vizsgalatok/prepast-hu/, https://pancreas.hu/en/studies/prepast). An intent to join is evaluated and approved by the organizing and steering committee of this study and the decision is made upon endoscopic experties in PPS implantation. The case report form (CRF) and the online electronic version (eCRF) have been developed (http://opr2.pancreas.hu/opr/forms/PREPAST). All the investigators receive an individual access codes to the eCRF.

An independent statistical company prepared the sample size calculation and the randomization lists. Finally, the study was started in 2017 with 4 participating centers.

9. RESULTS

9.1. Our research in PEP-prevention

9.1.1. PEP despite prevention with PPS, complications related to PPS, and different stent types

Our database contains data from patients collected between 2009 and 2014 in high volume endoscopy units of two large university teaching hospitals in Hungary. All ERCPs were performed by four experienced endoscopists (>200 ERCPs annually and ≥10 years ERCP experience). Indications of the ERCPs were obstructive jaundice, CBD stones on imaging studies, SOD type 1, acute cholangitis, known or suspected benign or malignant biliary stricture. All patients with acute biliary pancreatitis were excluded.

PEP incidence in different treatment groups:

PPS implantation was attempted in 317 high-risk patients out of 2462 ERCPs (12.9%). The mean age was 61.2 ± 16.5 years, and there were 209 females (65.9%).

PPS placement was successful in 288 cases (90.9%, “successful stent” group), but it was unsuccessful in 29 cases (9.1%, “unsuccessful stent” group). In our retrospective cohort from previous years there were 121 similarly high-rik patients without attempted PPS placement (“no stent” group). There were no significant differences among the groups in terms of PEP risk.

PEP occured in 29 patients (10%) in the „successful stent”, 12 patients (41.3%) in the „unsuccessful stent” and 38 patients (31.4%) in the „no stent” group. There were significantly

less PEP in the „successful stent" group, then in the other two groups ($p<0.005$), while the difference was not significant between these latter two ($p=0.3$).

Concerning PEP severity, all incidences in the subgroups of different severity forms of PEP were lower in the "successful stent" group, than in the other two, because the overall incidence was lower also (Figure 1, Table 2).

Figure 1: Incidence of different severity forms of PEP

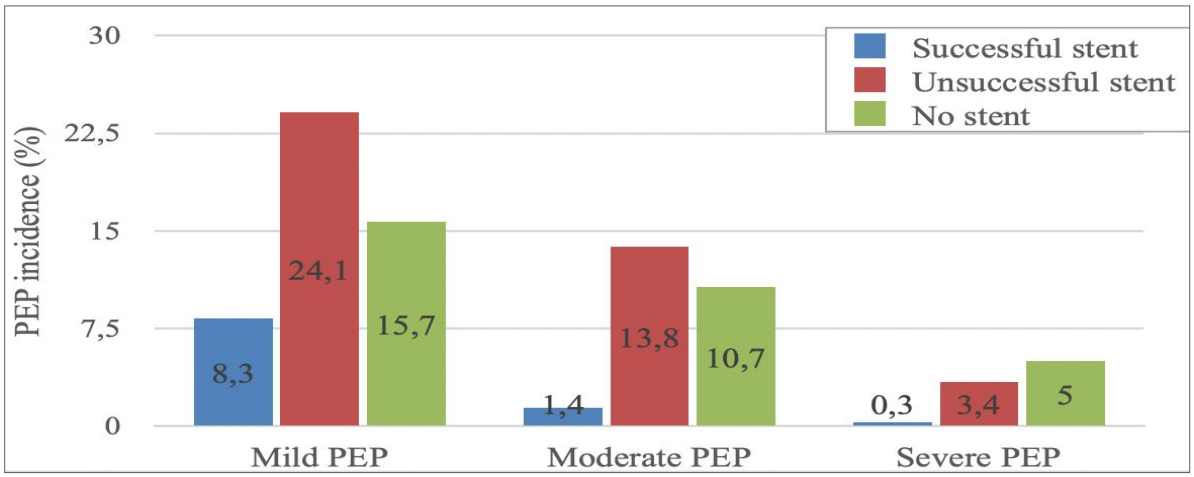


Table 2: Absolute numbers and distribution of each PEP severity in the study groups and the significance levels

Study groups (n)	**Mild PEP**	**Moderate PEP**	**Severe PEP**
Successful stent (n=288)	24	4	1
Unsuccessful stent (n=29)	7	4	1
No stent (n=121)	19	13	6
Distribution of PEP in each group (%)			
Successful stent (PEP=29, 10.0%)	82.8	13.8	3.4
Unsuccessful stent (PEP=12, 41.3%)	58.3	33.3	8.4
No stent (PEP=38, 31.4%)	50.0	34.2	15.8
Significance (*p*)			
Successful vs. unsuccessful	***0.006***	***<0.005***	***0.044***
Successful vs. no stent	***0.026***	***<0.005***	***<0.005***
Unsuccessful vs. no stent	0.284	0.644	0.731

PEP=post-ERCP pancreatitis; Note: significant differences are presented in bold, italic

PEP distribution was more favorable in the „successful stent" group, as the rate of moderate and severe PEP is significantly lower ($p<0,05$ in every case) compared to the other two groups. The differences between PEPs of different severity in the latter two groups are not significant (see Table 2).

PEP despite PD stenting:

Data of the "successful stent" group were further analyzed to detect any differences between the subgroups where PEP occurred ("PEP present") versus PEP did not developed ("PEP absent"). In the "PEP present" subgroup significantly more patient-related risk factor was present (Table 3).

Table 3: The mean of the sum of risk factors in the "successful stent" group

Successful stent group (n=288)	**PEP present (n=29)**	**PEP absent (n=259)**	***p***
Age (years)	57.5 ± 17.2	61.4 ± 16.4	0.23
Sum of all risk fators	5.62 ± 1.47	4.77 ± 1.44	**0.0029**
Sum of patient-related risk factors	3.76 ± 1.43	3.16 ± 1.23	**0.015**
Sum of procedure-related risk factors	1.86 ± 0.88	1.61 ± 0.98	0.19

Data represent the mean and standard deviation in each groups (mean±SD), significant *p* values are written in bold

The incidence rates of individual risk factors in the "PEP present" and "PEP absent" groups were examined. There were no significant differences except for SOD. Every individual risk factor was then analyzed with forest analyses using data mining methods to determine which factor has the most impact on developing PEP. The most important predictor of PEP when PPSs were used was the sum of "patient related risk factors", and SOD from individual risk factors.

Factors predisposing to unsuccessful stenting:

Data of "unsuccessful stent" group were also further analyzed. Significantly more patient-related risk factors were present in this group compared to the "successful stent" group (Table 4).

Table 4: The mean of the sum of risk factors in the study groups

High-risk study patients (n=317)	Successful stent (n=288)	Unsuccessful stent (n=29)	*p*
Age (years)	60.9 ± 16.5	64.2 ± 16.9	0.32
Sum of all risk fators	4.86 ± 1.47	5.38 ± 1.15	0.06
Sum of patient-related risk factors	3.22 ± 1.27	3.34 ± 1.23	0.61
Sum of procedure-related risk factors	1.64 ± 097	2.03 ± 0.80	**0.035**

Data represent the mean and standard deviation (mean±SD), significant *p* values are written in bold

Complications of PD stenting:

We observed early dislodgement and proximal migration during PPS usage, but other complications mentioned in the literature were not present in our study.

In high-risk patients, PPS should be in place for a minimum of 24 hours. Out of the 288 successfully stented patients, early stent dislodgment was observed in 5 (1.74%) which caused late onset PEP. All patients were symptom free for 8-12 hours, however developed PEP later on and their PPS were not in place under checking. There were 2 straight stents without an inner flange, and 3 Freeman-type stents (in the latter predisposing factors were always present: 1 post-papillotomy bleeding, 2 ballon dilations of the intact papilla).

In cases of proximal migration the stent slides into the PD and the outer end is not visible in the papillary orifice. There were 3 cases in our database (1.04%). All PPSs were straight with double inner and outer flange. In 2 patients, PPSs remained in place for longer than 1 month. The third patient had SOD. Two of the 3 were successfully removed, but it was unsuccessful in the 3rd case after multiple attempts, and finally the patient underwent a distal pancreatectomy.

Comparison of different stent types showed no significant differences in efficacy, but early stent dislodgment was observed with PPSs without inner flange, while proximal migration occurred with double inner flanged stents, although the number of complications was low.

9.1.2. Comparison of PPSs and NSAID suppositories

The effect of rectal NSAID and PPS in preventing moderate-to-severe PEP was compared in a network meta-analysis. 11 NSAID RCTs comprising 4296 patients and 10 PPS RCTs comprising 1239 patients defining and classifying PEP according to the Cotton criteria were included, separately analyzing the high- and average-risk population. The outcome of the included RCTs are summarized in Table 5.

Table 5: Outcome of the trials in our network meta-analysis

Author	Cont-rol (n=)	PEP in control group				Treat-ment (n=)	PEP in treatment group			
		All	Mild	Mod.	Severe		All	Mild	Mod.	Severe
Average-risk patients (NSAID studies)										
Sotoudehmanesh	221	15	10	-	-	221	7	7	0	0
Döbrönte 1	98	11	10	0	1	130	11	9	0	2
Otsuka	53	10	7	3	0	51	2	2	0	0
Katsinelos	260	27	19	6	2	255	12	10	2	0
Döbrönte 2	318	22	18	0	4	347	20	16	0	4
Patai	269	37	33	3	1	270	18	15	2	1
Ucar	50	7	3	4	0	50	1	1	0	0
SUM	***1269***	***129***	***100***	***16***	***8***	***1324***	***71***	***60***	***4***	***7***
High-risk patients (NSAID studies)										
Elmunzer	307	52	25	24	3	295	27	14	10	3
Katsinelos (subgroup)	203	25	18	5	2	188	11	9	2	0
Andrade-Dávila	84	17	14	3	0	82	4	3	1	0
Lua	75	4	4	0	0	69	7	4	3	0
Patil	200	23	14	5	4	200	6	6	0	0
SUM	***869***	***121***	***75***	***37***	***9***	***834***	***55***	***36***	***16***	***3***
NSAID SUM	**2138**	**250**	**175**	**53**	**17**	**2158**	**126**	**96**	**20**	**10**
Average-risk patients (PPS studies)										
Sofuni	103	14	8	6	0	98	3	2	1	0
Tsuchiya	32	4	2	1	1	32	1	1	0	0
SUM	***135***	***18***	***10***	***7***	***1***	***130***	***4***	***3***	***1***	***0***
High-risk patients (PPS studies)										
Tarnasky	39	10	5	5	0	41	1	0	1	0
Fazel	36	10	5	2	3	38	2	2	0	0
Harewood	8	3	3	0	0	10	0	0	0	0
Ito	35	8	8	0	0	35	1	1	0	0
Sofuni	204	31	22	8	1	203	16	12	4	0
Kawaguchi	60	8	8	0	0	60	1	1	0	0
Lee	51	15	12	2	1	50	6	5	1	0
Cha	58	8	3	2	3	46	2	2	0	0
SUM	***491***	***93***	***66***	***19***	***8***	***483***	***29***	***23***	***6***	***0***
PPS SUM	**626**	**111**	**76**	**26**	**9**	**613**	**33**	**26**	**7**	**0**

For NSAID studies, 7 RCTs with 2593 patients in the average-risk group and 5 RCTs with 1703 patients in the high-risk group were included.

For PPS studies, only 2 RCTs with 265 patients in the average-risk group, however 8 RCTs with 974 patients in the high-risk group were included. PPSs were placed intentionally with a success rate of 88-100%.

According to the results of our network meta-analysis, both in average- and in high-risk patients, only PPS reduces the risk of moderate to severe PEP significantly compared to placebo. Rectal NSAID compared to placebo and PPS compared to NSAID shows a clear trend but the difference was not significant (Table 6).

Table 6: League tables comparing the preventive methods

AVERAGE-RISK PATIENTS		
PPS		
RR: 0.12; [95% CI: 0.0033-1.2]	**NSAID**	
RR: 0.070; [95% CI: 0.0020-0.58]	RR: 0.58; [95% CI: 0.22-1.3]	**Placebo**
HIGH-RISK PATIENTS		
PPS		
RR: 0.32; [95% CI: 0.037-1.5]	**NSAID**	
RR: 0.19; [95% CI: 0.043-0.54]	RR: 0.57; [95% CI: 0.17-2.5]	**Placebo**

RR=relative risk, PPS=preventive pancreatic stent, NSAID=non-steroidal anti-inflammatory drug, CI=confidence interval

It is also remarkable, that not a single severe PEP case was reported in the PPS studies either in average- or in high-risk patients, but it was present in the NSAID studies (7/71 in average- and 3/55 in high-risk patients) (see Table 5).

Ranking probabilities based on surface under cumulative ranking (SUCRA) indicated that PPS placement had the highest likelihood of being ranked as the best treatment method in prophylaxis of moderate-to-severe PEP compared to rectal NSAID and placebo, both in average- and high-risk patient groups (average-risk: PPS 98%, NSAID 48%, placebo 4%; high-risk: PPS 96%, NSAID 45%, placebo 8%).

9.2. Our research in ABP

9.2.1. Non-randomized study

A total of 187 ABP patients were referred for ERCP between 1st January 2009 and 1st July 2010 in the two participating centers, but 46 patients had to be excluded (> 85 years old:

3, past history of gastric or pancreatobiliary surgery: 2, pancreatic abscess on initial CT: 2, liver cirrhosis: 10, INR >1.8: 5, >72 hours from symptoms: 8, failed biliary cannulation: 4, incomplete CBD clearance: 2, and insuccessful PD stenting: 4).

Finally, data of 141 patients were analyzed (100 female and 41 male; average age: 62.4 ± 15.1 years), from whom 71 had PPS insertion (PD stent group) and 70 had standard endoscopic therapy (control group).

There were no significant differences between the two groups in demography data (age, gender distribution), symptom-to-ERCP time, Glasgow score, length of hospital stay. They were also comparable regarding liver function tests, mean white blood cell counts, hemoglobin levels and peak serum amylase and CRP levels without significant differences. CBD stones were found in 70% of all cases.

PPS insertion was successful in 94.7% (71 of 75 cases). The patients in whom PD stent insertion was attempted but failed did not develop any serious. Minor post-papillotomy bleeding occurred in two patients (one in each groups), that were managed endoscopically.

Outcome of ABP:

ABP complication occurred in 9.86% in the PD stent group (7/71 cases; 1 MODS transmitted to intensive care unit, 2 sepsis, 3 large pseudocysta, 1 surgical necrosectomy). No mortality was observed in this group.

In the control group complication occurred in 31.43% (22/70 cases; 4 MODS requiring ICU transmission, 4 sepsis, 10 large pseudocysts, 1 surgical necrosectomy). Three patients died; two in the early phase, because of severe, uncontrollable MODS, while the third patient after 21 days because of septic shock. The mortality rate was 4.28% (3/70 patients).

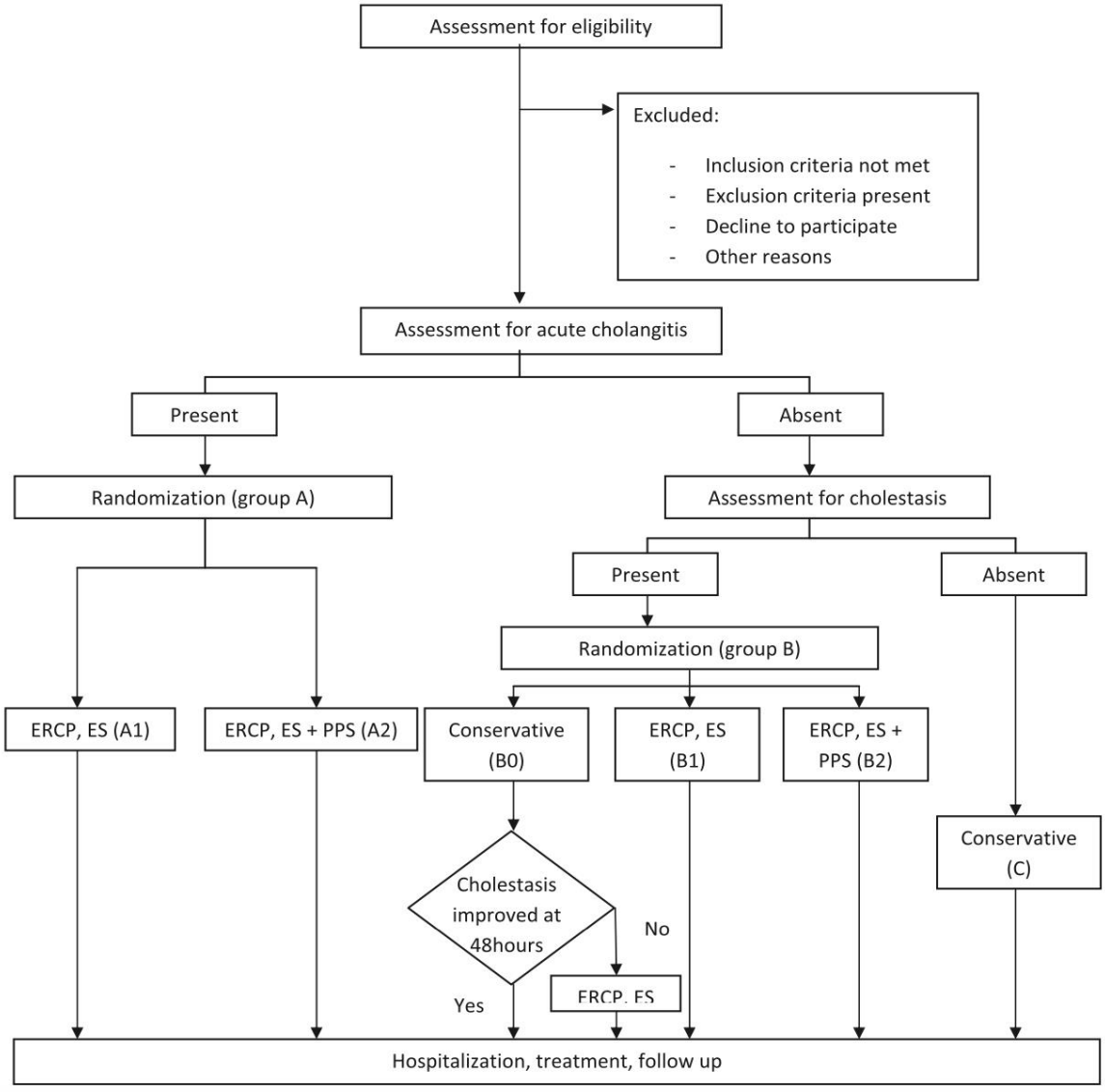
The overall complication rate was significantly lower in the PD stent group (9.86 vs. 31.43%, $p<0.002$). There was a trend toward a higher mortality rate in the control group compared to the PD stent group (0 vs. 4.28%), but because of the low case number it did not reach the level of significance.

9.2.2. Randomized study

The outcome of the PPS group in our non-randomized study was significantly better, than in the control group, so we hypothesized that PPS not only prevents the potentially harmful effects of ERCP, but it may reverse the process of ABP in the early phase. Therefore we developed a randomized controlled trial, which is called Prepast study (PREventive PAncreatic STents in the management of acute biliary pancreatitis).

ABP patients are categorized into two groups. When coexisting acute cholangitis is also present, they form group A. These patients should undergo urgent ERCP according to the international guidelines. They are randomized into two therapeutical subgroups (standard treatment of EST and CBD stone extraction: A1, or standard treatment+PPS: A2) with an allocation ratio of 1:1. Patients without signs of cholangitis are assessed for evidence of cholestasis (ERCP is "probably indicated" category in the guideline). These patients (group B) are randomized into 3 subgroups with an allocation ratio of 1:1:1 (standard treatment: B1, or standard treatment+PPS: B2, conservative treatment: B0). Those patients in whom signs of cholestasis are absent (group C) are exluded (Figure 2).

Figure 2: Randomization folwchart in the Prepast study



The primary endpoint of the study is the percentage of ABP patients with complicated courses in the different treatment groups (standard endoscopic therapy group: A1+B1, and the standard therapy with PPS implantation group: A2+B2). The complicated course was described by a composite endpoint (moderate and severe AP, any systemic and/or local complications, and mortality). Study-specific secondary endpoints were on one hand related to the outcome of ABP, on the other hand related to the endoscopic therapy.

Patients are assigned an identification number consisting of 5 numbers and 1 letter. The first two numbers are the center identification number, then the letter is the group identifier, finally the last three numbers are the patient-specific randomization number (eg. 01-A-001).

Basic treatment principles are: initial goal directed intravenous fluid resuscitation with isotonic crystalloid solution (lactated Ringer is preferred), decision of oral refeeding or nasojejunal feeding on day two after hospitalization, and avoidance of preventive antibiotic therapy. Contrast-enhanced abdominal CT is required in 72-96 hours from the onset of pain in patients with a suspicion of severe or complicated course of ABP. Any further therapeutic decisions are left to the discretion of treating gastroenterologist. A patient is discharged from hospital if they become symptom free and tolerate oral feeding, and is scheduled for an outpatient follow-up in 3 months. Those, who are treated with nasosejunal feeding, but become stable, also discharged home, but scheduled for follow up in every 2 weeks until final decision for intervention (eg. drainage, surgery) has been made. A final follow up is scheduled three months after the intervention.

Sample size calculation is based on the results of our previous non-randomized study and with a 5% rate of lost to follow up, so 230 patients should be enrolled in this study (115 in both, PPS and control study arms). A safety interim analysis is scheduled at 50% enrollment status, which we have just achieved, as the centers have enrolled 141 patients so far, of whom 22 were assigned to the conservative (B0) arm, so 119 cases were assigned to one of the intervention subgroups planned to be analyzed (A1, A2, B1, B2).

10. DISCUSSION

10.1. Our research in PEP prevention

In the first part of our scientific work, we examined the effects of PPSs on PEP. We demonstrated the beneficial effect of PPSs in high-risk patients compared to non-stented and unsuccessfully stented patients. Not only the lower incidence of PEP could be observed, but

significantly less moderate and severe pancreatitis developed in the stented group than in the other two, in other words PPS placement shifted this complication towards milder cases.

We were the first to describe in the literature, that in patients with preventive PD stenting, certain risk factors are as likely to be present in the subgroup that developed PEP as in those who did not, and only SOD was an exception. Based on these results, we concluded that PPS implantation (excluding SOD) prevents the effects of various risk factors. We also found that patients who developed PEP despite PPS placement had significantly more patient-related risk factors than those without PEP, but there was no significant difference in the number of procedure-related risk factors. The risk carried by each patient appears to be more important, so we recommend that the risk of PEP should be assessed very accurately before the ERCP.

However, if PPS insertion is attempted but remains unsuccessful, significantly more procedure-related risk factors were present in the subgroup of patients who developed PEP, while the number of patient-related risk factors did not differ in the two groups. In other words, more complex, more difficult procedures are more likely to end up in failure of PPS implantation. In our own practice, in cases of difficult cannulation, if the guidewire enters the PD, it is not removed, but the ERCP is continued with either PPS implantation or a double-guidewire technique, especially if the patient is (also) at high-risk of PEP. Unsuccessful stenting has an especially high risk of PEP. Freemant and colleagues described this risk as 66.7%, although this conclusion was based only on data of 3 patients. In our database we have almost ten times more, altogether 29 unsuccessfully stented patients, and we found a PEP incidence of 41.3% after analyzing these data, which was not significantly different from the “no stent” group of high-risk patients (31.4%). We can say, that with appropriate routine, there is no need to be afraid of PPS insertion, but there is no literature data on the extent to which stenting can/should be enforced.

We also examined the complications of PPS usage. In our own material, only early dislodgment and proximal migration were observed, but rarely, in roughly 1% of all cases. Late onset PEP draws attention to early stent dislodgment (or occlusion). Pancreatic stents without inner flange or an ERCP-complication (eg. post-papillotomy bleeding) are tend to cause early dislodgment. A repeated PPS implantation, the so called rescue ERCP can be beneficial for these patients. Proximal migration, although not more frequent complication, but more unfavorable for the patient, because removal of those stents can be challenging and can sometimes fail. Predisposing factors based on the literature are SOD, long (> 7 cm) stents and/or stents with double inner flanges, while the outer pigtail (or partial pigtail) end is preventive. In our study, we only observed this complication with straight, double inner flange stents. We

didn't found a single case when using Freeman-type stents, thus, in our experience, this appears to be the safest to use.

In the next part of our research, we examined the preventive effect of NSAID suppositories and PPSs in the prophylaxis of moderate-to-severe PEP. For a patient, if severe PEP develops, it can lead to severe complications or even death. In our research, the incidence of moderate-to-severe PEP was significantly lower with PPS compared to placebo, but not to rectal NSAID suppositories. However, PPS is the more preferred prophylaxis based on SUCRA results. These results are valid in both average- and high-risk patient groups. It is noteworthy, that none of the RCTs in our analysis showed severe PEP formation in the PPS group, whereas they did in the rectal NSAID group.

10.2. Our research in ABP

There was a great debate over decades about the advantages and necessity of ERCP in ABP patients. Endoscopic therapy should be performed at the early phase, in 48-72 hours from the onset of pain, because the organ failure initiated by the inflammatory cytokines cannot be influenced afterwards. There is a very narrow time interval for performing ERCP, as it takes 9-15 hours from the onset of symptoms to hospitalization. Severity of AP also cannot be predicted in the very early phase, because diagnostic elevation of parameters used or appearance of radiology signs takes 2-3 days.

When examining the effect of ERCP on ABP we should not neglect the fact, that the endoscopic procedure itself can cause AP or can worsen its severity. In that sense an ABP patient is considered high-risk. Furthermore, those ERCPs performed in ABP are technically more difficult, than in acute cholangitis for example. Although patomechanism of ABP is not fully understood even nowadays, but PD obstruction, increased intrapancreatic duct pressure and early, intraductal enzime activation is among the proposed steps, therefore, theoretically, relieving the obstruction, lowering the intraductal pressure and drainage of pancreatic fluid with PPSs similar to PEP prevention can improve the outcome of ABP.

In the first part of our research, PPS implantation was performed in those ABP patients, in whom the ERCP and bile duct cannulation was difficult. We hypothesized, that PPS placement can compensate the negative effect of difficult cannulation similarly to prevention of PEP. The results of our study were more favorable, as the results of the PPS group were much better, with significantly less complication rate and although not significant, but clearly lower mortality, compared to EST and CBD stone extraction. Based on these results, we could not only demonstrate for the first time in the literature, that in ABP patients PPS implantation

is safe, feasible and effective, but also it can prevent the unfavorable effect of difficult cannulation which can aggravate AP. Furthermore, as the results were even better than the standard endoscopic treatment, we hypothesized, that PPS placement not only can prevent the harmful effect of papilla manipulation, but by lowering the intrapancratic duct pressure and maintaining the outflow of pancreatic juices, it can manipulate the inflammatory cascade and evolution of ABP into a more favorable direction.

Based on these results, we developed a protocol for a randmoized trial, the Prepast study. Under the auspices of HPSG, this was the first randomized, controlled trial. The study examines the effects of ERCP performed in the early stages of ABP, and compares the effects of standard endoscopic treatment with standard treatment+PPS implantation on the outcome of AP. Hopefully we will be able to demonstrate the beneficial effect of PPS implantation in the ABP patient population, but at least the safety of the intervention. It is important to mention, that PPS implantation should be performed in the early phase. A Finnish study showed significantly more infectious complications, when pancreatic stenting was performed in the late phase, in cases of pancreatic necrosis. Our results are expected to provide additional result or clarify the timing of PPS implantation.

11. CONCLUSIONS

Our research on PPS can be divided into two main parts, on one hand, on the role of PPS in PEP prevention, and on the other hand, on the use of PPS in ABP.

In the first part of our work, we demonstrated, that the use of PPSs reduces the incidence of PEP in the high-risk group, and in addition PEP has a more favorable course compared to no stenting. We have also shown, that PPS protects against the harmful effects of almost all known risk factors, except for SOD. Development of PEP despite PD stenting should be expected if the individual patient has more patient-related risk factors, while in the case of more difficult ERCP procedure, i.e., more procedure-related risk factors, PPS implantation can be unsuccessful. Out of the used pancreatic stents, a PPS with a single inner flange and an outer pigtail end appears to be the safest to use. The results of our network meta-analysis show, that PPS is more likely to prevent the development of moderate-to-severe PEP in both moderate- and high-risk patients, than NSAID suppositories or placebo.

In the second part of our work, we demonstrated that PD stenting performed in the early phase of ABP, within the therapeutic window (in 72 hours), is safe, and even provides better outcomes than no stenting during ERCP. We hypothesize, that this beneficial effect can be

demonstrated not only in cases of difficult cannulation, but also in a randomized manner. The study is ongoing and the results of the interim analysis are expected in the near future.

12. SUMMARY / NEW RESULTS

1. In an analysis of our prospectively collected database of high PEP risk patients undergoing PPS implantation for PEP prevention, we demonstrated that PPS application significantly reduces the risk of PEP carried by the known risk factors. We are the first in the literature to show that PPS, with the exception of SOD, protects against the adverse effects of known PEP risk factors.
2. Our data show, that patients at high-risk of PEP are significantly less likely to develop PEP with PPS, and if they do develop PEP, it is milder than in patients whose stenting has failed, or have not been stented.
3. We showed, that although unsuccessfully stented high-risk patients develop significantly more PEP than successfully stented patients, this incidence is not significantly higher compared to the non-stented cases.
4. We have demonstrated, that patients who develope PEP despite PPS implantation have significantly more individual risk factors than those who did not develop PEP; and that patients with failed PPS implantation have significantly more procedure-related risk factors (ie. more complex ERCP), than those who were successfully stented.
5. We have been published in the literature for the first time in a large case-series, that if PPS insertion was not performed during the first ERCP, and the patient develops severe PEP symptoms, PPS implantation during a “rescue ERCP” performed 8-20 hours after the first ERCP prevents severe PEP complications.
6. In a network meta-analysis we have compared the preventive effect of the two most commonly used PEP prophylactic methods, NSAID suppositories and PPS, for moderate and severe PEP, and found PPS to be a more effective preventive method in both the average- and high-risk groups.
7. Another new finding is that no severe PEP occurred in the stented group in either the average- or high-risk groups in the examined studies, but this was not the case for NSAID suppositories, where a few severe PEP cases have been published.
8. Based on our prospective database, the prophylactic efficacy of the different types of PPS we used did not differ, but the type with a single inner flange and an outer pigtail end seems to be the most optimal in terms of stent-related complications.

9. For the first time in the literature, we published the beneficial effect of PPSs on complications and disease progression in a patient population with ABP where endoscopic intervention (EST and biliary stone extraction) proved difficult.
10. Based on these results, we were able to demonstrate for the first time in the literature not only that PPS implantation in the ABP patient population is safe and effective, but also that it can prevent the adverse effects of difficult cannulation.
11. Based on these results, we have also developed the protocol for the Prepast RCT, to investigate the efficacy of PPS added to ERCP and EST in early ABP, and this is the first RCT in the international literature on this topic. The trial is ongoing and interim analysis results are expected in the near future.

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