Analysis of the quality indicators, advanced biliary cannulation techniques and difficulty of endoscopic retrograde cholangiopancreatography (ERCP)

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1. INTRODUCTION

1.1. History, current applications, and quality indicators of ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential minimal invasive procedure in the treatment of several biliary and pancreatic disorders. We see a trend that with the advancement of technology, gastrointestinal endoscopy might obviate the need for more invasive surgical interventions.

The European and American Society of Gastrointestinal Endoscopy (ESGE and ASGE) developed their quality indicators for ERCP practice. These measures include pre-, intra-, and post-procedural elements to ensure safe and effective practice world-wide.

1.2. ERCP Registries

Clinical patient registries are getting essential tools of healthcare in the 21st century. These databases enable us to gather easily analyzable data on diseases, procedures related to healthcare, which could potentially lead to better, more efficient and cost-effective patient care.

1.3. Difficult biliary cannulation, advanced cannulation methods and ERCP in acute biliary pancreatitis cases

In about 20-30% of ERCPs, biliary access is difficult and the risk for adverse events increases, therefore the choice of proper cannulation technique is essential. In these situations, an advanced cannulation method should be used to access the bile ducts. If the pancreatic duct is cannulated more than once, a pancreatic guidewire-assisted technique could be used more easily. The double guidewire method, transpancreatic sphincterotomy and prophylactic pancreatic stent-assisted methods are the most widely used techniques to choose from. When the pancreatic duct is not accessed then a precut method e.g., traditional needle knife precut papillotomy or fistulotomy could be used.

In acute cholangitis (AC), early achievement of biliary drainage is associated with better outcomes, especially in the severe, septic cases as stated in the new 2018 Tokyo guideline for acute cholangitis. In acute biliary pancreatitis (ABP), the role of ERCP is more ambiguous, when AC is also present early intervention is indicated, however, in cases with temporary biliary obstruction only, the need for an early ERCP is questionable. There are some attempts to objectively grade the difficulty of ERCP, e.g., in the consensus-based ASGE grading system cases of acute pancreatitis get a higher, 3 out of 4 points. However, no supporting data was found to this classification claim besides the consensus.

2.AIMS

1. The first aim was to develop a useable ERCP Registry System in Hungary since no structured data collecting systems were used in our country for this purpose. First single-center, then multicenter monitoring of quality indicators was planned.
2. Difficult biliary cannulation is a major challenge in ERCP, to achieve biliary access, advanced cannulation methods are used. We aimed to compare the cannulation success rate, adverse events rate of different advanced cannulation techniques by systematic literature review and meta-analytical methods.
3. We intended to analyze data from the Hungarian ERCP Registry to quantify the difficulty of ABP cases compared to AC cases without pancreatitis.

3. METHODS

3.1. Methods for AIM 1 (ERCP Registry)

3.1.1. General considerations

Center for Translational Medicine, University of Pécs and the Hungarian Endoscopy Study Group initiated the Hungarian ERCP Registry in 2016. The development of the registry was a major development in the monitoring of ERCP practice in Hungary.

Data from the Hungarian ERCP Registry database was extracted to be analyzed in this study. At the point of analysis, 7 tertiary referral centers and 18 endoscopists uploaded data into the Registry. Consecutive patient enrollment was expected from all participating endoscopists. Cases from 09/2016 till 04/2019 were included in this study. A follow-up call after 30 days was carried out to discover late adverse events. In our registry, a 4-step checking system is used to ensure data quality: (1: local check from an administrator, 2: endoscopist, 3: central check by the chief administrator, 4: registry coordinator (ÁV)) (more information can be found at https://tm-centre.org/en/registries/ercp-registry/). The Scientific and Research Ethics Committee of the Medical Research Council approved the Hungarian ERCP Registry (TUKEB-35523/2016/EKU).

3.1.2. Inclusion and exclusion criteria

All available and quality checked, 3260 ERCP cases in the registry at the point of analysis were included. Subgroup analysis, according to e.g., native papillary status, advanced cannulation cases were executed.

3.1.3. Statistical analysis

Continuous measures are summarized and presented as means and standard deviations (SD) or as median and interquartile ranges (IQR). Categorical data are presented as observed and as percentages. To determine differences between continuous parameters, depending on the distribution of the data, we used the independent Student's t-test or the Mann–Whitney U test for two groups. We used the Chi-square test or Fisher's exact test to analyze the relations between the factors under examination and odds ratios were also calculated. All analyses were performed with SPSS 25 statistical software (IBM Corporation, Armonk, NY).

3.2. Methods for AIM 2 (Comparison of advanced cannulation techniques)

3.2.1. Search Strategy

A systematic literature search was conducted to find all relevant articles containing data on TPS following the PRISMA guideline. The search strategy included the following terms: "transpancreatic septotomy" or "transpancreatic sphincterotomy" or "transpancreatic septostomy" or "transpancreatic precut sphincterotomy" or "pancreaticsphincterotomy" or "transpancreatic papillary septotomy" or "transpancreatic sphincter precut" or "transpancreatic duct precut" or "pancreatic sphincter precutting" or "pancreatic precut sphincterotomy" or "transpancreatic precut septotomy" or "transpancreatic precut septostomy" or "pancreatic septotomy" or "pancreatic septostomy" or "pancreatic precut" or "transpancreatic precut" or "transpancreatic." EMBASE, PubMed, Scopus, Web of Science, ProQuest, and Cochrane Library databases were searched from their inception till February 8, 2018.

3.2.2. Inclusion Criteria

To compare TPS to DGW and NKPP, only prospective studies were included. However, only retrospective data were available in the comparison of TPS–NKF, and these were also included in our analysis. Appropriate conference abstracts were also analyzed to minimize publication bias, and additional subgroup analyses excluding them were carried out to show their effects on outcomes. Comparative and also non-comparative prospective and retrospective studies were included in the calculation of overall success and complications rate of TPS. Randomized controlled trials (RCT) and prospective and retrospective observational studies were analyzed separately.

3.2.3. Risk of Bias Assessment

The Newcastle–Ottawa scale (NOS) was used for prospective and retrospective studies to assess the risk of bias within the individual studies. Randomized controlled trials were assessed by the Cochrane Risk of Bias Tool.

3.2.4. Statistical Methods

Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to compare the biliary cannulation success and PEP rates among the different cannulation techniques. Risk difference (RD) was calculated to compare the bleeding and perforation rates to avoid overestimation since OR or RR calculations would exclude those studies where zero events were reported. The random-effect model of DerSimonian and Laird was used in meta-analysis. Subgroup analyses excluding studies with sequential designs and that reported only in an abstract format were also carried out. Sensitivity analyses were carried out using four types of summary statistics (RR [risk ratio] vs. OR vs. RD vs. Peto's OR) and two types of meta-analytical models (fixed vs. random effects) to test the robustness of our findings. Heterogeneity was tested with two methods, namely the Cochrane's Q and the I^2 statistics. The Q test was computed by summing the squared deviations of each study's estimate from the overall meta-analysis estimate; P values were obtained by comparing the statistical results with a χ^2 distribution with k−1 degree of freedom (where k was the number of studies). A P value of less than 0.1 was considered suggestive of significant heterogeneity. The I^2 statistic represents the percentage of the total variability across studies that is due to heterogeneity, i.e., I^2 value between 0 and 40% indicates low, 30–60% moderate, 50–90% substantial, and 75–100% considerable heterogeneity, based on Cochrane Handbook for Systematic Reviews of Interventions. Publication bias was planned to be examined by visual inspection of funnel plots and the Egger's method. Meta-analytical calculations were done with Review Manager (RevMan) computer program (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3.3. Methods for AIM 3 (Difficulty of ERCP in ABP and AC)

3.3.1. General cohort from the Hungarian ERCP Registry

Prospectively collected data from the Hungarian ERCP Registry were analyzed in this cohort study comparing ABP and AC cases. The Hungarian Endoscopy Study Group initiated the project of the Hungarian ERCP Registry in 2016 and the number of participating centers growing gradually since then. Cases from 7 tertiary referral centers and 15 endoscopists were uploaded into the Registry. Quality indicators laid down by ESGE and ASGE were mostly met by our centers showing general good practice of ERCP, only NSAID suppository usage was significantly lower, while bleeding and perforation were somewhat higher than expected. All participating endoscopists uploaded all ERCP cases which were done by them consecutively, no trainee participation was recorded. Recruitment period lasted from 09/2016 till 04/2019. A

30-day telephone follow-up, data quality check and ethical approval was carried out as detailed in Section 3.1.1.

3.3.2. Statistical analysis

Basic statistical methods were used as detailed in Section 3.1.5. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors from the followings: age, gender, study groups (ABP vs AC), JPD and ASA score for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) where significant differences were detected, and enough data was available. All analyses were performed with SPSS 25 statistical software (IBM Corporation, Armonk, NY).

4. RESULTS

4.1. Results for AIM 1 (ERCP Registry)

4.1.1. General characteristics of the cohort

First, a single-center pilot study was carried out in our hospital analyzing data from the first year of the Registry. This showed the general usability of the registry system (37). 3260 ERCP procedures were done on 2573 patients, from that 1909 ERCPs (58.6%) were carried out on native papilla patients. Most patient had only 1 ERCP in the database while there were also patients with 5-9 registered procedures. From all ERCPs, 1434 (44.0%) were done on males and 1826 (56.0%) on female patients. Average age of patients was 68.2 years (range: 2 – 103 years, SD: 15.5 years, average of male patients: 68.0 vs. female: 68.4 years).

Average bodyweight of the male patients was 82.9 kg vs. 70.6 kg of females. Average height was 172.6 cm in man while 161.2 cm in women. Average BMI was 27.8 kg/m^2 in men and 27.2 kg/m^2 in women. Most of the patients were ASA class 1 and 2 (2532/3260, 77.7%). ASA 1 class patients were significantly younger than ASA 2, 3 or 4 patients. Anticoagulation or antiplatelet medication use was more common in ASA 2, 3 and 4 patients compared to ASA 1.

Patients with juxtapapillary diverticula were older (77.4 vs. 66.9 years), but gender distribution was similar (14.9% in men vs. 14.7% in women).

4.1.2. Indications of ERCP

Most of ERCPs were carried out for biliary indications (3179/3260, 97.5%), pancreatic indications were rare (81/3260, 2.5%). Obstructive jaundice (31.0%), diseases of the bile ducts (32.2%) and acute cholangitis (25.9%) were the most common biliary indications. No significant differences could be observed in the distribution by gender or age.

Pancreatic indications were done for pancreatic duct disease (0.6%), for suspicion of pancreatic malignancy (0.7%) and for the evaluation of chronic pancreatitis or pseudocysts (1.1%).

4.1.3. Objective grading of ERCP difficulty

More than half of all ERCP cases were grade 2 (51%, n=1663), 31% were grade 3 (n=1018) and only 15% were grade 1 procedure according to the ASGE grading of ERCP complexity. The most difficult procedures with grade 4 were rare with only 3% (n=81) of all cases.

In grade 1 procedures biliary cannulation was unsuccessful in 1.4% of cases, while it was significantly higher in grade 2 (8.2%) and in grade 3 cases (7.0%), but the number of unsuccessful cannulation cases stayed below 10%. A significantly higher number of unsuccessful cannulation cases could be seen in the grade 4 ERCPs with 35.5% of all cases. Post-ERCP pancreatitis rate was not higher in the more complex grades; however, bleeding (3.7%) and perforation (1.2%) were more common in grade 4 cases.

4.1.4. Biliary cannulation success rates

Biliary cannulation was successful in 92.6% (2943/3179) of all cases with biliary indication while 91.3% (1710/1872) in native papilla cases, while the success rate reduced to 88.1% (897/1018) in difficult biliary cannulation cases. After the use of advanced cannulation methods in 85.8% (738/860) of the cases successful biliary access was achieved. The overall cannulation rate was above 90% in all centers, but there were some variations in the cannulation success of native papilla cases and even more in cases of difficult biliary access.

4.1.5. Advanced cannulation methods

In 759 cases at least one advanced cannulation method was used. In 40.2% (305/759) of advanced cannulation cases successful biliary access was achieved in less than 5 minutes. from the beginning of the cannulation.

4.1.6. Adverse event rates

Post-ERCP pancreatitis (PEP) rate of all cases was 1.6% (53/3260), while in cases with native papilla was 2.5% (48/1909) and it was 3.1% (32/1045) in difficult biliary cannulation cases. The severity of PEP was mild in the majority of cases (n=38, 71.7%), moderate in 22.6%, while severe in 5.7%.

Clinically significant bleeding occurred in 0.9% (30/3260) of all cases, in native papilla cases it was 1.1% (21/1909), while in difficult cannulation cases it was 1.4% (15/1045). 50% of all significant bleeding events were mild, 43.3% were moderate severity and only 2 cases required 2 or more units of blood transfusions and classified as severe bleeding complications.

Perforations occurred in 0.6% (19/3260) of all ERCPs, mostly developed in native papilla patients (0.9%, 17/1909). Ten perforations were registered in difficult cannulation cases (1.0%, 10/1045). Out of all perforation cases 9 were mild not requiring prolonged hospitalization (47.4%), however 10 cases (52.6%) required longer hospital stay (4-10 days) (14). Only one case required surgical operation due to perforation by the tip of the endoscope. Guidewire caused perforation (Stapfer type III) in six cases, in 11 cases periampullary perforation (Stapfer type II) occurred during sphincterotomy (one perforation occurred after ampullectomy) and in one case distant perforation (Stapfer type I) was recorded.

Post-ERCP cholangitis developed in 74 patients (2.3%). 83.8% of them was mild and only required antibiotics, while re-ERCP was needed to resolve cholangitis in 16.2% of the cases.

Hypoxia were observed in 2.3% (75/3260) of all ERCPs and hypotension during procedure was recorded only in 2 patients.

The use of advanced cannulation techniques did not increase the PEP, clinically significant late bleeding and perforation rates compared to simple cannulation native papilla cases, while intraprocedural bleeding was significantly higher in the advanced cannulation group.

4.1.7. Post-ERCP pancreatitis prophylaxis

Indomethacin suppositories were administered in 47.4% (1546/3260) of all cases, while in cases with native papilla the use of NSAID increased to 57.2% (1092/1909), and it was similar to the latter in difficult cannulation cases (57.4%, 600/1045). 24 PEP developed in cases where no NSAID suppository was given, out of them unfortunately 1 was severe and 5 PEP was moderately severe. 9 PEP developed in the 243 ERCPs with multiple pancreatic cannulations (3.7%). Only 44% of these cases was a PPS placed, 6 PEP developed in patients without PPS (6/135, 4.4%), while with PPS only 3 PEP was registered (3/108, 2.8%).

4.1.8. Cannulation times

Average cannulation time was 184 s if all cases are included, cannulation time increased to 249 s in native papilla cases, and in patients with difficult biliary cannulation it was 439 s, above the 5-minute margin. Cannulation was achieved after 5 minutes in 470 cases, 15 PEP developed (3.2%) in these cases.

An increasing trend could be seen with prolonged cannulation times in simple cannulation cases in PEP and procedural bleeding rates. PEP rate increased from 0.6% in the <120 sec cannulation

group to 2.1% in the 120-300 sec group (p=0.002), while clinically significant bleeding is 0.5% in the <120 sec groups and 1.7% in the groups >120-300 sec (p=0.01).

4.1.9. Fluoroscopy times

Average fluoroscopy time was 126 sec. In most centers, fluoroscopy time was in the 90-130 sec range. However, in 2 centers average fluoroscopy time was considerably longer, 166 sec and 284 sec.

4.1.10. Quality indicators of ERCP practice

Most quality indicators were met; however, perforations and bleeding complications rate were higher than the expected target. Follow up was only successful in 71.6% of cases, which should be improved to detect delayed adverse events.

There was a high variability in the use of indomethacin suppositories among centers (1.7-91.7% of all cases). In one center PEP rate was unexpectedly high, 20.4%.

In two centers, the rate of successful cannulation in native papilla cases were 0.6-2.6% lower than the 90% threshold.

4.2. Results for AIM 2 (Comparison of advanced cannulation techniques)

4.2.1. Study selection

Altogether, 2787 records identified during database searching: 510 in EMBASE, 339 in PubMed, 968 in Scopus, 255 in Web of Science, 544 in ProQuest and 171 in Cochrane Library, respectively. The latest search was run on February 8, 2018, and finally 33 relevant studies were included in the qualitative synthesis, while data from 14 studies were extracted for the meta-analysis.

4.2.2. Characteristics of studies included

Three RCTs and two prospective observational studies reported comparable data about TPS vs. DGW. One of them was only available in abstract form. Two of them used a sequential design, applying TPS only after DGW, as a rescue technique.

Two RCTs and three prospective, observational studies provided data on the comparison of TPS vs. NKPP, two of them with sequential design, no new prospective studies were identified compared to our previous meta-analysis, however, additionally, we conducted further sensitivity and subgroup analyses in this comparison.

Comparison of TPS and NKF was not found in any prospective studies, in this estimation four retrospective studies (two of them only in abstract form) were analyzed to synthesize available comparative evidence.

Two prospective case series of TPS without relevant comparisons to other advanced cannulation methods and, additionally, 23 retrospective observational studies with reported outcome data were included in the pooled analyses of overall outcomes of TPS.

4.2.3. Methodological quality and risk of bias assessment

The risk of bias in the prospective (not RCTs) and the four retrospective studies included in the meta-analyses were analyzed with the NOS. In most of the full-text studies baseline characteristics of cohorts were reported with comparable, homogeneous groups. Technical details of interventions were thoroughly reported, all full-text studies defined precut methods appropriately. On the other hand, definitions of adverse outcomes were not the same in all the studies. However, most of them used the consensus definitions. The appropriate length of follow-up is questionable in the cases of late adverse events, only one prospective study reported the length of follow-up as longer than 30 days. All abstracts lacked information about most of the above-mentioned details, therefore they are of high risk of bias.

In case of RCTs, the Cochrane Risk of Bias Tool was used. Only one study reported the method of randomization and the method of ensuring allocation concealment. Blinding in studies of endoscopic interventions at participant and personnel level is difficult to execute, and therefore could not be expected. However, blinded late outcome assessment (PEP, late bleeding, perforation) could be arranged more easily. Nevertheless, none of the studies reported blinding (masking) of any kind. Three out of 5 RCTs did not report the rate of cholangitis, therefore this outcome could not be analyzed. One RCT was published only in abstract form which makes the data quality questionable, consequently, this study was of high risk of bias.

Publication bias could not be reliably assessed based on funnel plots or by the Egger's method because of the small number of included studies. According to the Cochrane Handbook funnel plots and other statistical tests are not advised to assess small study effect and publication bias under ten studies per analysis.

4.2.4. Endoscopists' experience and centers' case volumes in the prospective studies

Most of the prospective studies reported endoscopists' experience in yearly case numbers, some also described lifetime ERCP numbers. Based on the reported numbers, all endoscopists performed more than 200 ERCPs/year. In one study, the case load of the endoscopists exceeded 500 ERCPs annually. Trainee participation was not reported in any of the studies. Most of the centers reported high-volume ERCPs (even above 1000 procedures/year, only one study reported lower numbers (<300 ERCPs/year), while no information was found about center or endoscopist case load in one studies.

4.2.5. Biliary cannulation success rate

TPS showed superiority in success rate compared to DGW (OR 2.72; 95% CI 1.30-5.69; 176 and 235 patients, respectively; I^2 =50%) and NKPP (OR 2.32; 95% CI 1.37-3.93; 292 and 260 patients, respectively; I^2 =7%). The success rate of TPS and NKF did not differ (OR 1.38; 95% CI 0.32-5.96; 295 and 141 patients, respectively; I^2 =22%).

In the TPS vs. DGW comparison of cannulation success rates, no significant difference was detected between the two methods (OR 3.02; 95% CI 0.73-12.59; 113 and 107 patients, respectively; I^2 =69%), if only RCTs were included, probably because of the greater confidence intervals of the results. On the other hand, subgroup analysis of full-text studies found the superiority of TPS over DGW with regard cannulation success rate.

The overall success rate of TPS in prospective studies was 89.7% (564/629). The success rate was the same if all studies were analyzed (89.6%, 2343/2615), as well as the separate analysis of RCTs were resulted similarly high value (91.7%, 199/217).

4.2.6. Post-ERCP pancreatitis

No significant difference was found between the TPS vs. DGW (OR 0.72; 95% CI 0.24- 2.10; 151 and 134 patients, respectively; I^2 =55%) and TPS vs. NKPP (OR 1.63; 95% CI 0.48-5.47; 265 and 242 patients, respectively; I^2 =57%) comparisons. However, the TPS technique showed a higher PEP rate compared to NKF method (OR 4.62; 95% CI 1.36-15.72; 295 and 141 patients, respectively; I^2 =16%).

If we excluded abstracts from the NKF vs. TPS comparison, the significant difference disappeared (OR 3.49; 95% CI 0.20-62.21; 86 and 115 patients, respectively; I^2 =63%) and expectedly, a wide confidence interval could be seen. In the other subgroups, no differences were found when sequential studies or abstracts were omitted from the analyses. Exclusive inclusion of RCTs did not result in a change in significance regarding TPS vs. DGW and TPS vs. NKPP comparisons.

The overall PEP rate of TPS was 8.1% (49/604) in prospective studies, 7.1% (183/2590) in all studies, and 7.4% (16/217) in RCTs.

4.2.7. Prophylactic pancreatic stent and NSAID suppository use

Only one recently published study used PPS in all patients undergoing TPS, while all the others reported no or only some PPS implantation in the TPS cases. NSAID suppositories were not used or not reported in any of the prospective studies included in the meta-analyses.

4.2.8. Bleeding

The pooled analysis did not show any difference in bleeding rate when TPS were compared to DGW (risk difference [RD] 0.01; 95% CI -0.03-0.05; 109 and 95 patients, respectively; I^2 =0%), NKF (RD 0.00; 95% CI -0.03-0.03; 295 and 141 patients, respectively; I^2 =0%) and NKPP (RD -0.00; 95% CI -0.03-0.04; 268 and 239 patients, respectively; I^2 =20%).

Subgroup analyses did not alter the findings of bleeding rates significantly.

The overall bleeding rate of TPS was 3.4% (19/562) in prospective studies, 2.0% (50/2548) in all studies, and 1.7% (3/175) in RCTs.

4.2.9. Perforation

Perforation rates did not differ when comparing TPS vs. DGW (RD -0.01; 95% CI -0.04-0.03; 109 vs. 95; I^2 =0%), TPS vs. NKPP (RD -0.00; 95% CI -0.02-0.01; 267 and 240 patients, respectively; I^2 =0%) and TPS vs. NKF (RD 0.00; 95% CI -0.02-0.03; 295 and 141 patients, respectively; I2 =0%).

Subgroup analyses did not alter the findings in perforations rates significantly.

The overall perforation rate was 0.5% (3/562) in prospective studies, 0.4% (11/2548) in all studies, while 0% (0/175) in RCTs.

4.2.10. Sensitivity and subgroup analyses

Application of other meta-analytical models (fixed effects vs. random effects analysis) and summary statistics (OR vs. RR vs. RD vs. Peto's OR) did not affect the outcomes significantly in the main analyses, thus, our conclusions remain unaltered.

However, subgroup analyses excluding non-RCTs, sequential trials and studies only available in an abstract form significantly altered some results (i.e., success rate in TPS vs. DGW and PEP rate in TPS vs. NKF comparisons, respectively).

4.2.11. Follow-up

Pancreatic duct stricture or chronic pancreatitis could potentially develop after pancreatic sphincterotomy, therefore a longer follow-up period to detect these adverse outcomes is needed. Small caliber pancreatic stents could rarely cause pancreatic ductal changes in long-term (1 month or longer). Only one prospective study, a case-series with 116 patients reported a median 5-month follow-up (range 2-35) with no late adverse events. Another paper similarly did not report late chronic pancreatitis or ductitis from PPS, no strictures were described during longer,

however not specified follow-up. A few retrospective studies also published longer term results: Miao et al. reported no stricture after four months of follow-up period, while Barakat et al. found no late stricture formation after an unknown length of "long-term" follow-up.

4.3. Results for AIM 3 (Difficulty of ERCP in ABP and AC)

4.3.1. General characteristics of the cohort

AC patients were significantly older than ABP patients, while more women were in the ABP group (63.1 vs. 69.6 years, $p<0.001$). A higher proportion of ASA I patients was in the younger ABP group, while more ASA III patients were in the older AC group. No significant difference was found in the anticoagulation and antiplatelet use between the two groups. Interestingly, more juxtapapillary diverticula were observed in AC patients (26.8% vs. 12.9%, $p<0.001$).

4.3.2. Findings of ERCP

Normal cholangiogram was observed more frequently in ABP than in AC cases (20.0% vs. 12.3%, $p=0.026$). Dilated common bile duct (CBD) without stone or sludge was found during ERCP in a higher proportion of ABP patients, compared to AC patients (22.6% vs. 12.8%, respectively, $p=0.005$). Biliary sludge without stones and small CBD stones (≤10 mm) were found equally frequently in ABP and AC group (14.3% vs. 9.1% ($p=0.073$) and 39.1% vs. 46.9% ($p=0.088$), respectively). Large CBD stones were present more commonly in AC patients (3.9% vs. 18.9%, $p<0.001$). Expectedly, purulent bile was more frequently found in AC cases than in ABP cases (6.5% vs. 22.2%, $p<0.001$).

4.3.3. Biliary cannulation success rates

Successful biliary access was achieved in ABP cases in 230/240 (95.8%) vs. 243/250 (97.2%) in AC cases ($p=0.409$) during the initial ERCP. Simple cannulation succeeded less frequently in the ABP group (54.6% vs. 75.6%; $p<0.001$), however, no difference was found in the success rate of advanced cannulation methods in the two groups (91.7% vs. 88.5%; $p=0.503$).

4.3.4. Advanced cannulation methods and post-ERCP pancreatitis prophylaxis

Advanced cannulation methods were used in 108/240 (45.0%) cases of ABP, while only in 61/250 (24.4%) of AC cases ($p<0.001$). Multiple advanced methods were used in 13/61 in AC and 30/108 in ABP cases, respectively ($p=0.354$). More pancreatic duct manipulations were found in the ABP group (31.3% vs. 17.2%, $p<0.001$) and also more prophylactic pancreatic stents were inserted in these patients (19.6% vs. 4.8%; $p<0.001$). No difference was seen in the NSAID suppository use between the two groups (67.1% vs. 62%; $p=0.240$).

Carrying out a binary logistic regression for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) did not change ORs significantly by the adjustment.

4.3.5. Adverse event rates

Only a low number of clinically significant bleeding (0% vs. 0.8%), perforation (0.8% vs. 1.2%), cholecystitis (1.3% vs. 1.6%), immediate bleeding cases (9.6% vs. 7.2%) were detected, and no significant difference could be detected between the groups in this regard.

4.3.6. Cannulation times

The average biliary cannulation time was significantly longer in the ABP group (248 sec vs. 185 sec, p=0.043), however, that difference could not be found when the simple (113 sec vs. 116 sec) or the advanced cannulation time (409 sec vs. 396 sec) were separately analyzed. The number of more than 5-minute cannulation was higher in the ABP patients (28.2% vs. 19.3%; p=0.037), and with normal cholangiograms, the cannulation lasted longer in the ABP group (324 sec vs. 154 sec; p=0.040). This difference could also be seen in patients without JPD (261 sec vs. 158 sec, p=0.005).

4.3.7. Fluoroscopy time

Fluoroscopy time was longer in the AC group, when all cases (91 sec vs. 107 sec; p=0.009), and the simple cannulation cases (91 sec vs. 107 sec; p=0.008) were compared. When stone extraction was done in AC patients, it took significantly longer, most probably due to the higher rate of larger (>1 cm) stones (89 sec vs. 107 sec; p=0.009). In other subgroups, no differences were found.

5. DISCUSSION

In this study, we report initial multicenter data from a newly initiated ERCP Registry in Hungary. The goal of the project to monitor performance and quality indicators and to support prospective research initiatives as a platform. Seven, high-volume centers reported data, and further centers also expressed their interest to join to the Registry. Here we found that this Registry is suitable to monitor the most important performance measures and most quality indicator goal are met. However, there is room for improvement in PEP prophylaxis, indomethacin and also pancreatic stents should be used more consistently following guidelines by every centers. According to our data, with the use of advanced cannulation methods PEP

and late bleeding rate was similar to simple cannulation in native papilla cases, while intraprocedural bleeding was more frequent with the use of advanced cannulation methods.

This study has a number of strengths, here we present a high case number, prospectively collected registry data from seven Hungarian tertiary centers. There is more quality check built-in that should limit incorrect data entry and underreporting.

Some limitations of the study should be mentioned. All participating hospitals and endoscopist were high-volume and case distribution varied among centers that hinder generalizability.

In the future, we plan to expand the registry to all centers that perform ERCP in Hungary. These plans to monitor quality indicators could direct efforts to ensure safer ERCP practices possibly in lesser number of hospitals with higher levels of expertise and case numbers. Prospective, observational studies and also randomized controlled trials could be developed on the basis of the registry. With the expanding infrastructure and backing by the community of endoscopist we are considering many directions of research in the field (e.g. ERCP training, post-ERCP pancreatitis prophylaxis, advanced cannulation methods).

The second project is a systematic review and meta-analysis which show that TPS could be equally successful or even slightly better in the setting of difficult biliary access compared to other advanced cannulation methods. Analyzing only the prospective studies, with regard to cannulation success rates TPS seem superior to DGW and NKPP while TPS and NKF are equally effective. DGW and NKPP carry a similar risk of PEP compared to TPS; however, PEP occurs more frequently with TPS than with NKF. No difference in bleeding and perforation rates were found when comparing TPS to the other advanced cannulation methods.

Whenever possible, we only analyzed prospective observational studies and RCTs to gain the best evidence. Heterogeneity between the studies was low or moderate in most analyses, making our conclusions more accurate. Sensitivity analyses and applying different statistical and meta-analytical methods did not reveal any significant changes in the main associations. However, subgroup analyses excluding sequential studies revealed that the significant difference disappeared in some analyses, thereby weakening our conclusion in the success rate of TPS vs. DGW and PEP rate in TPS vs. NKF. However, this is most probably the result of the low case numbers leading to imprecision and wider confidence intervals.

A new Scandinavian RCT published in 2021 comparing TPS vs. DGW concluded that TPS achieved higher rate of successful biliary access than DGW while PEP rate was not significantly

different between the two techniques. Prophylactic pancreatic stents were used only in 8.7% and 11.1% in the two groups and a considerably high PEP rate was registered with 13.5% and 16.2%. Including this new RCT in our previous meta-analysis of successful biliary cannulation and PEP rate, analyzing only RCTs a significantly better success (RR 1.22, 1.03-1.40, p=0.02) and not significantly lower PEP rate (RR 0.65, 0.37-1.15, p=0.14) was found in the TPS group.

There are several limitations of our analyses. First of all, the low number of prospective studies with only small cohorts of patients weakens the conclusions. Sequential studies were also included which could alter our results. However, in the comparison of DGW or NKPP vs. TPS, sequential designs could affect the TPS cannulation success and adverse event rate only to the worse. The lack of information on the use of preventive methods (PPS, NSAID suppositories) undermines the assessment of PEP rates. New studies are lacking in this field with the consistent use of PPS and NSAID suppositories. It should be noted, however, that the PEP rate was only 1.1% in the study of Sugiyama et al, where all patients received PPS after TPS, compared to the rate of 7.1% pooled from all studies where most patients did not have PPS. Besides that, the definitions of outcomes were not standardized in all cases. Nonetheless, most prospective studies used the consensus definitions. Publication bias cannot be ruled out due to the low number of studies per analysis.

In the cases of sequential studies, exceptionally low cannulation rates (as low as 72%) and high PEP rates (36.8%) could be seen, that could be probably explained by the previous DGW attempts which should be avoided to minimize papillary trauma and consequential edema. For that reason, we recommend using the TPS technique as first choice.

The overall cannulation success rate of TPS is close to 90% (67.9%-100%) in all studies and subgroups by study designs, which makes this pancreatic guidewire assisted method a successful alternative to DGW. The overall success of DGW is only 63% in the studies where TPS was also used. While a meta-analysis of 7 RCTs with DGW successful cannulation was achieved in 82% of cases. The average cannulation success rate of NKPP seems to be approximately 80% (647/812) in our previous meta-analysis of all NKPP studies and 77% (201/260) in prospective studies.

PEP rate of TPS is similar to other advanced cannulation methods (7.1%; 183/2590; 0-30%), NKF however could be better to avoid PEP. With the uniform use of PPS and NSAID suppositories in all TPS cases PEP rate might be even lower as the significant protective effect of PPS has been well proven. Importantly, its insertion should not be problematic since the

guidewire is already in the pancreatic duct while performing TPS. In this regard, NKPP seems comparable to TPS with its 8.8% overall PEP rate measured in our previous meta-analysis. Bleeding rate of TPS is in the range of 2-4%, which is comparable to the widely accepted and frequently used needle knife precut techniques (4%; 30/745 if all NKPP studies included) (53). The rate of perforation was around 0.5% which is remarkably low for a precut technique, and no difference was found in this respect between TPS and the other advanced cannulation techniques.

The possible benefit of TPS over the free-hand precut techniques is that it is a wire assisted method, with better controlled cut. For that reason, it could be appealing to beginners and the PPS insertion could be also easily achieved with the guidewire inside the pancreatic duct. In the unfortunate cases when TPS fails additional needle-knife incision could be helpful at times to reach deep biliary cannulations and should be used as salvage technique in the appropriate situations.

The third part, an analysis of the ERCP Registry data to address the issue of difficulty of ERCP in acute biliary pancreatitis. Our data support the ASGE grading of difficulty for pancreatitis in ERCP. Several parameters suggest that ERCP is more challenging in ABP cases than in AC cases. We found that the rate of advanced cannulation method, and the rate of inadvertent pancreatic cannulation were higher, the cannulation time was longer in ABP patients than in AC cases. These observations point to the fact that we face difficult biliary cannulation in ABP more frequently compared to AC cases, where similar pathologic changes related to the biliary tree are expected. Importantly, the cannulation success rate and the rate of adverse events were not influenced by this. We also found a higher number of cases with normal cholangiogram in the ABP group (20.0%) compared to AC (12.3%). In these cases, spontaneous passage of stones or sludge by the time of ERCP is one possible explanation for the initial worsening of cholestatic parameters. Additionally, this also might be due to the difficulty of diagnosing acute cholangitis when acute pancreatitis is also present, but also can be explained by the suboptimal availability of preprocedural endoscopic ultrasound evaluation in the participating Hungarian centers. ERCPs could have been avoided in these cases, cost and avoidable invasiveness should be highlighted, as a potential benefit.

Our study has several strengths, first of all, it is a quite large, prospectively collected, nationwide dataset from several centers in Hungary. Consecutively collected ABP and AC cases were available in almost equal numbers with good data quality, detailed data set, and in an appropriate sample size. Secondly, our registry system has a built-in quality assurance

program that could limit false data entry and underreporting. Multivariable statistics also confirmed the robustness of our findings.

There are some limitations to our study. Post hoc questions raised in a prospective registry database might result in confounding effects. All cases come from high-volume centers and endoscopists, and case distribution is varied among centers that hinder generalizability. The inherent biases of observational studies and retrospective designs e.g., selection bias should be noted in our study as well. There were some differences between the two groups, firstly, AC patients were older, and had more comorbidities (more ASA III patients). Secondly, more juxtapapillary diverticula were found in the AC group. For this reason, binary logistic regression model was used to adjust for these differences. Thirdly, the differentiation of AC cases in the ABP group could not have been done due to the lack of reliable guidelines or tools to confirm the presence of cholangitis in ABP. We were curious about the additional worsening effect of ABP on AC and non-AC cases, but we could not reliably separately analyze AC+ABP and ABP cases without AC. These factors could somewhat limit our analysis.

Based on our data, ABP cases should be handled by more experienced endoscopists who are familiar with a wide range of cannulation techniques, pancreatic guidewire assisted (DGW and TPS), as well as needle knife precut techniques. To lower the worsening effect of inducing more pancreatic edema, the insertion of a PPS might potentially improve disease course.

6. CONCLUSIONS

An easy-to-use ERCP Registry system has been developed with great prospect in quality assurance, monitoring of training and licensing. We provide the results of the first multicenter data analysis of the Hungarian ERCP Registry which showed a generally good practice of ERCP in the participating high-volume centers. Some improvement in the field of PEP prophylaxis (e.g., NSAID suppository and pancreatic stent use) could be expected in the future by disseminating the results of this analysis.

Based on the results of the systematic review and meta-analysis, the late adverse events of TPS, e.g., pancreatic duct stricture and chronic pancreatitis, could not be assessed properly because only one study reported a longer-term (more than 30-day) follow-up with no late adverse events. We think that follow-up studies should be extended up to one year or longer to detect late adverse events, e.g., pancreatic stricture formation or the development of chronic pancreatitis. These findings show the short-term safety and efficacy of TPS and also highlight the necessity of long-term follow-up studies after precut papillotomies.

The grade 3 difficulty classification by ASGE seems to be justified for the ABP cases, and these patients should not be left to the less experienced endoscopists. Additionally, determining the appropriate indication of ERCP is vital in ABP patients. Hence, we would like to emphasize the need for the broader application of less invasive diagnostic tools (e.g., endoscopic ultrasound) in this patient population to decrease the number of unnecessary ERCPs.

7. NEW RESULTS

1. We carried out the first multicenter data analysis of the Hungarian ERCP Registry, which provides data on quality indicators, cannulation techniques, success and adverse events. A generally good practice was registered in the participating centers. A pilot study with single center data has been published to get attention to this project in Hungary. According to our multicenter results, the use of PEP prophylaxis methods (NSAID suppositories and pancreatic stents) was underutilized, and the rate of perforations were higher than the expected target levels. With the dissemination of the results, we aim to achieve a better adoption of the current guidelines.
2. We carried out the first systematic review and meta-analysis of the TPS and other advanced cannulation methods. We did ancillary analyses to our previous meta-analysis published in Endoscopy. This article is cited in the ESGE guideline on ERCP-related adverse events. We provide evidence on the potential effectiveness and safety of TPS which is an underutilized method among the advanced cannulation techniques. TPS cannulation success rate was higher than DGW and NKPP while NKF was equally effective in this regard. PEP occurs more frequently with TPS compared to NKF, but DGW and NKPP carries a similar risk of PEP compared to TPS. No difference in bleeding and perforation rates were found when comparing TPS to the other advanced cannulation methods. Based on this recommendation TPS might be used more frequently in expert centers. However, to get the final conclusion further randomized controlled studies are needed.
3. We provide the first evidence that ERCP in ABP cases are objectively more difficult than in similar cases with only AC. This is based on the results that the rate of advanced cannulation method uses, and the rate of inadvertent pancreatic cannulation were higher, the cannulation time was longer in ABP patients than in AC cases. The consensus-based grade 3 classification of ERCPs in ABP cases is justified based on our data.

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9. SCIENTOMETRICS

Publications and metrics rely on the MTMT2 and Google Scholar, the data were extracted on 28th January 2021.

Scientific papers:

- Total: 32
- English-language: 28

Impact factor (since 2016):

- First author: 16.324
- Cumulative: 97.121

Citations (since 2016):

- Cumulative: 356 (MTMT: 259)
- Hirsh index: 13 (MTMT: 11)

10.LIST OF PUBLICATIONS

Papers upon which this thesis relies (n=5, cumulative impact factor: 13.573, cumulative citation: 22):

1. **Pécsi D**, Hegyi P, Szentesi A, Gódi S, Pakodi F, Vincze Á. [The role of endoscopy registries in quality health care. The first data from the Hungarian Endoscopic Retrograde Cholangiopancreatography (ERCP) Registry]. Orv Hetil. 2018; 159(37):1506–15. DOI: 10.1556/650.2018.31145 (**Q3, IF: 0.564, cited: 2**).
2. **Pécsi D**, Tóth M, Vincze Á. Endoszkópos regiszterek a minőség szolgálatában. MAGYAR BELORVOSI ARCHIVUM 2019; 72 (2): 95–100. (**cited: 0**)
3. **Pécsi D**, Farkas N, Hegyi P, Varjú P, Szakács Z, Fábián A, Varga G, Rakonczay Z, Bálint ER, Erőss B, Czimmer J, Szepes Z, Vincze Á. Transpancreatic sphincterotomy is effective and safe in expert hands on the short term. Dig Dis Sci. 2019; 64: 2429–2444. DOI: 10.1007/s10620-019-05640-4 (**Q1, IF: 2.751, cited: 5**)
4. **Pécsi D**, Farkas N, Hegyi P, Balaskó M, Czimmer J, Garami A, Illés A, Mosztbacher D, Pár G, Párniczky A, Sarlós P, Szabó I, Szemes K, Szűcs Á, Vincze Á. Transpancreatic sphincterotomy has a higher cannulation success rate than needle-knife precut papillotomy-a meta-analysis. Endoscopy 2017; 49(9): 874-887. DOI: 10.1055/s-0043-111717 (**Q1, IF: 6.629, cited: 15**)
5. **Pécsi D**, Gódi S, Hegyi P, Hanák L, Szentesi A, Altorjay I, Bakucz T, Czakó L, Kovács G, Orbán-Szilágyi Á, Pakodi F, Patai Á, Szepes Z, Gyökeres T, Fejes R, Dubravcsik

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Papers loosely related to the topic of the thesis (n=3):

1. **Pécsi D**, Vincze Á. Az endoszkópos retrográd kolangiopankreatográfiát követő pancreatitis megelőzésének lehetőségei. MAGYAR BELORVOSI ARCHIVUM. 2019; 72 (5): 246–251. (**cited: 0**)
2. Halász A, **Pécsi D**, Farkas N, Izbéki F, Gajdán L, Fejes R, Hamvas J, Takács T, Szepes Z, Czakó L, Vincze Á, Gódi S, Szentesi A, Párniczky A, Illés D, Kui B, Varjú P, Márta K, Varga M, Novák J, Szepes A, Bod B, Ihász M, Hegyi P, Hritz I, Erőss B, Hungarian Pancreatic Study Group. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis. Dig Liv Dis. 2019; 51(9): 1281-1286. DOI: 10.1016/j.dld.2019.03.018 (Q2, IF: 3.570, cited: 9)
3. **Pécsi D**, Vincze Á. Are Suprapapillary Biliary Stents Superior to Transpapillary Biliary Stents?. Dig Dis Sci, 2020 (65): 925–927 (Q1, IF: 2.751, cited: 0)

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