The macroscopic appearance of the major duodenal papilla influences bile duct cannulation – a prospective multicenter study by the Scandinavian Association for Digestive Endoscopy (SADE) study group for ERCP.

Background

How to best achieve a safe and effective bile duct cannulation during endoscopic retrograde cholangio-pancreatography (ERCP) has always been, and still is, a much-debated issue[1–3]. Both technical- and patient-related aspects of cannulation and cannulation difficulties have previously been investigated[4–6], but not if, and in what way, the endoscopic appearance of the major duodenal papilla may influence cannulation.

All endoscopists who perform ERCP recognize the obvious differences in the macroscopic appearance of the major duodenal papilla[7]. This has led to a widespread conception among endoscopists that certain specified appearances of the papilla are more difficult to cannulate and therefore more prone to complications[8–12]. However, until now there has not been a structured investigation of what kind of influence the macroscopic appearance of the major duodenal papilla has on difficulties during bile duct cannulation.

Before determining the association between the macroscopic appearance of the major duodenal papilla and cannulation difficulties some prerequisites have to be met. Firstly, there has to be a clear definition of what is to be considered a difficult bile duct cannulation in order to make any evaluation of cannulation difficulties relevant and reproducible. There have been several different definitions utilized to investigate this matter[13]. However, since 2016, the European Society for Gastrointestinal Endoscopy (ESGE)[14] recommends the use of the definition presented in the SADE group study[15] when investigating issues regarding difficult bile duct cannulation. This definition shows a clear increase in complications when any of the criteria of: more than 5 min, five attempts or two pancreatic guide-wire passages were met.

Secondly, to make certain that different endoscopists are in agreement on the endoscopic appearance of the papilla, an interobserver-validated endoscopic classification has to be established. In our previously published paper, the first inter- and intraobserver-validated classification of the endoscopic appearance has been presented[16], see Figure 1.

With a validated classification and an accepted definition of difficult cannulation in place, we aim to determine the possible influence the endoscopic appearance of the major duodenal papilla has on the ability to perform bile duct cannulation during ERCP.

Methods

Patients from nine different centers in the Nordic countries, that, on clinical grounds, were scheduled for ERCP were prospectively included into the study. To be included the patients had to be over 18 years old, have an intact, naïve, major duodenal papilla and that the desired duct to cannulate is the common bile duct.

Exclusion criteria were a papilla hidden inside a large diverticulum or bulky tumors of the papilla that made classification impossible and also patients with surgically altered anatomy.

Primary outcome measure was differences in the frequency of difficult cannulation distributed between the different papilla types. Difficult bile duct cannulation was defined using the 5-5-2 criterion, i.e. after 5 min, five attempts or two pancreatic guide-wire passages and when any of those limits

is reached[15].The endoscopic appearance of the major duodenal papilla was classified into one of the four distinctive papilla types: Regular (Type 1), Small (Type 2), Protruding or Pendulous (Type 3) and Creased or Ridged (Type 4) of our previously published classification[16], see Figure 1. When, during the ERCP, the duodenoscope reached the papillary region in the duodenum, the endoscopist classified the endoscopic appearance of the papilla into one of the four predefined papilla types. Two photographs of the papilla were captured with and without a cannulation catheter or sphincterotome alongside it for size reference. Thereafter, bile duct cannulation was initiated. Time was recorded from the first intentional touch of the papilla. The number of continuous contacts with the papilla, attempts, were recorded as well as all guide-wire passages into the main pancreatic duct. When a guidewire or catheter was securely placed inside the common bile duct, determined by fluoroscopy, the stopwatch was terminated. The number of cannulation attempts and pancreatic guide-wire passages was summarized. Data regarding the indication for the ERCP, patient demographics, methods used for cannulation, measures taken to avoid post ERCP pancreatitis (NSAIDs and/or

protective pancreatic endoprosthesis insertion) as well as post-ERCP complications occurring during the first 24 hours or before discharge were recorded. Complications were defined according to the consensus criteria[17]. No further follow-up of the severity of the complications were made.

To determine the influence of endoscopists experience on difficulties during bile duct cannulation of the different papilla types, endoscopists of different levels of experience were allowed to start cannulation attempts. When an inexperienced endoscopist, i.e. a "fellow", started attempting bile duct cannulation and could not achieve deep bile duct cannulation within 5 min a more senior colleague replaced the fellow and continued cannulation efforts. A fellow was defined as an endoscopist having performed less than 200 career-long ERCPs[18]. Expert endoscopists were defined as having made over 1000 ERCPs, and intermediate endoscopists, 200-1000 ERCPs, during their career. Power calculations were not possible since the distribution of the different papilla types was previously unknown as was the overall frequency of difficult cannulation using the ESGE approved definition. In the SADE group

study[15] where the current definition of difficult cannulation was created, only expert endoscopists participated.

All statistical calculations were made with SPSS version 25. Chi-square test or, Fisher exact test were used for categorical data as appropriate, as well as odds ratio calculation. Mann-Whitney U-test was used for non-normally distributed continuous data.

The study was approved by the ethical review board at the Karolinska Institutet, Stockholm (Dnr 2013/908-31/2).

Results

In total, 1401 patients were included in the study. Classification of the papilla into the predefined types was possible in 98% of the cases. In 2% (n=24) of the cases, the endoscopist was unable to select an appropriate papilla type and these 24 cases were excluded from further analyses. The endoscopist was asked to state a reason for inability to classify the papilla. In the majority (n=13) of cases a swollen papilla caused by inflammation, impacted stones or an unexpected finding of a tumor (exclusion criteria) was indicated as the causative factor. In five case reports, no explanation for inability to perform

classification was given. It was in violation with the study protocol to classify the papillae in retrospect using the photos taken during the ERCP. In only one case did the endoscopist have problems in choosing between the defined papilla types. In the remaining five cases classification was impossible due to inability to find the papilla either because of extensive mucosal folds, large diverticulum (exclusion criteria), or narrow duodenal lumen hindering movement of the duodenoscope.

The distribution of the different papilla types is shown in Figure 2, with regular papilla, Type 1 being the most frequent (56%) followed by Type 3, protruding or pendulous papilla occurring in 23%.

The mean age of the patients was 66 years (range 18-101 years) and 52% were female. The most common indications for ERCP were common bile duct stones 44%, followed by periampullary tumor[19] ~~and jaundice, see Table 1. No significant differences was~~ (excluding tumors invading the papilla itself) and jaundice, see Table 1. No significant differences were seen between the different papilla types regarding age, sex, previous cholecystectomy rate, NSAID use, protective pancreatic stent or indications for ERCP, except for

patients with creased or ridged papilla, Type 4. Compared with Type 1 papilla, patients with Type 4 papilla were, on average, younger (mean 59 years vs 66 years, $p<0.0001$) and had more frequently primary sclerosing cholangitis as an indication for ERCP (18.7% vs 5.7%, $p<0.0001$). In patients with Type 3 papilla, periampullary diverticulum was not as frequent as in Type 1 papilla (6% vs 13%, $p=0.001$).

In most instances the cannulation attempts were started by an expert endoscopist (n=870, 62%) and to a lesser extent by an endoscopist in the intermediate category (n=240, 17%). In 291 cases (21%), a fellow started the cannulation attempts. The level of endoscopist experience was evenly distributed among the different papilla types, with only minor, non-significant differences.

The overall frequency of difficult cannulation regardless of papilla type was 42% (95% CI 39-44%). Among the different papilla types, difficult cannulation varied, as shown in Figure 3. Small papilla, Type 2 (52%, 95% CI 45-59%) and protruding or pendulous papilla, Type 3 (48%, 95% CI 42-53%) were significantly more often difficult to cannulate compared to regular, Type 1

papilla (36%, 95% CI 33-40%). There was, accordingly, an increased odds ratio (OR) for difficult cannulation for both small papilla (OR=1.89, 95% CI 1,37-2.62) and protruding or pendulous Type 3 papilla (OR=1.61, 95%CI 1,24-2,10) compared with regular, Type 1 papilla. Creased or ridged, Type 4 papilla (43%, 95% CI 34-52%) did not show any significant difference from regular Type 1 papilla in the frequency of difficult cannulation.

Cannulation difficulties were even more evident when endoscopists with different levels of experience attempted bile duct cannulation. Regardless of papilla type, bile duct cannulation was more often difficult when a fellow started (69%, 95% CI 64-74%) as well as when an endoscopist from the intermediate category started (49%, 95% CI 42-55%) compared when an expert started (30%, 95% CI 27-34%, both p-values <0.0001). The frequency of difficult cannulation for endoscopists with varying degrees of experience are shown in Table 2. ~~Although more experienced, among experts there was still a significant increase in OR for difficult cannulation when comparing regular, Type 1 papilla to small, Type 2 papilla (OR=2.28, 95% CI 1,50-3,49).~~ If only analyzing Experts endoscopists performing bile duct cannulation on their own

also shows a significantly higher frequently of difficult cannulation when cannulating small papilla, Type 2 (43%, 95%CI 34-53%, p=0.0002) or protruding or pendulous papilla, Type 3 (36%, 95%CI 29-43%,p=0,0075) compared to regular papilla, Type 1 (25%, 95%CI 21-29%). No difference was seen for creased or ridged papilla, Type 4 (32%, 95%CI 21-45%, p=0.22). The median time to successful bile duct cannulation was significantly longer for both Type 2 papilla (Median time 269 sec, IQR 622 sec) and Type 3 papilla (Median time 245 sec, IQR 794 sec) compared to Type 1papilla (Median time 139 sec, IQR 455 sec, both p<0.05). Cannulation time for creased or ridged papilla Type 4 (Median 210 sec, IQR 515 sec) was not significantly different from Type 1.

In 99% of the ERCPs the endoscopists used guide-wire assisted cannulation. If cannulation became difficult, 50% of the endoscopists continued with guide-wire cannulation until cannulation succeeded or failed. In the remaining patients, different auxiliary cannulation techniques were used. Standard pre-cut technique as the only auxiliary method was used in 9%, pancreatic sphincterotomy in 15%, double wire technique in 15% and combination of

several techniques in 10%. No significant differences between the papilla types regarding choice of auxiliary technique was found.

The overall post ERCP pancreatitis (PEP) frequency regardless of papilla type was 6.7% (95%CI 5.5-8.2%). When there was difficult cannulation the frequency of PEP frequency increased to 8.9% compared to 5.1% (p=0.006) when cannulation was not difficult. There was also a variation in the frequency of PEP between the different papilla types but none of the differences were statistically significant. Regular, Type 1 papilla had a PEP frequency of 6.1% (95%CI 4.6-8.0%) whereas small, Type 2 papilla had 9.4% (95%CI 5.9-14.6%), protruding or pendulous, Type 3 papilla 6.4% (95%CI 4.1-9.7%) and creased or ridged, Type 4 had 7.5% (95%CI, 3.6-14.3%). There was overall a low frequency of other complications such as post-interventional bleeding (0.2%) and cholangitis (0.6%) and there were no significant differences between the papilla types.

The overall frequency of failed cannulation was low (2.8%, 95% CI 2.1-3.9%), with only non-significant differences between the different papilla types. However, the frequency of failed cannulation regardless of papilla type

increased from 1.9% to 6.3% ($p<0.0001$) if a fellow started cannulation attempts compared to an expert, even though they had to turn the endoscope over to a more senior colleague after 5 min. This was especially pronounced for small, Type 2 papilla with an overall 14% failed cannulation frequency when a fellow started compared to 2.7% ($p=0,018$) when an expert performed the cannulation single-handedly. The OR, regardless of papilla type, for failed cannulation when a fellow started to cannulate compared to when an expert endoscopist started was 4.0 (95% CI, 2.0-8.2, $p=0.0001$). When a fellow started the OR for failed cannulation on a small papilla was 6.1 (95%C.I 1.4-27, $p=0.017$) and on a protruding or pendulous papilla 5.2 (95% CHI 1.3-21, $p=0.022$) compared to when an expert started.

Discussion

Although many endoscopists have been assuming that the appearance of the major duodenal papilla has implications on bile duct cannulation no prospective investigation of this matter has previously been performed. By utilizing our classification of the endoscopic appearance of the major

duodenal papilla combined with the ESGE approved definition of difficult cannulation, we have determined that small, Type 2 papillae and protruding or pendulous, Type 3 papillae are more frequently difficult to cannulate. Accordingly, they also have a higher OR for difficult cannulation compared to regular, Type 1 papillae. These findings have previously only been assumed, based on expert opinion, and not on a validated classification of different papilla types and a prospective data collection[4,11,12]. With these results in mind, further research regarding cannulation difficulties has to take these aspects into consideration.

In addition, this study demonstrates clear differences regarding frequency of difficult cannulation, between a fellow starting cannulation of a certain type of papilla, compared to when an expert is starting. This finding is, of course, obvious, but has previously not been quantified using the present definition for difficult cannulation or in regard to differences in endoscopic appearance of the papilla types. The differences in frequency of difficult cannulation might also be of use when evaluating competence among different endoscopists and during ERCP training. With beginners having a high ratio of difficult

cannulation and experts a significantly lower ratio, and as difficult cannulation is a considerably more frequent phenomenon than failed cannulation and affects every endoscopist to a varying degree, it can be used as an intraprocedural quality measure along with failed cannulation frequency[20,21]. Further studies regarding this might determine a benchmark for what frequency of difficult cannulation one should accomplish and maintain to be considered a qualified ERCP endoscopist.

A more unexpected but intriguing and important finding is that when a fellow starts cannulation the odds for failed cannulation increase significantly even as a more senior endoscopist continues cannulation attempts after 5 min. These findings also have implications on how education and training in ERCP and bile duct cannulation is conducted. For example, it may be suggested that when a fellow is confronted with a certain papilla type, i.e. small, Type 2 or protruding or pendulous, Type 3 papilla, they probably should abstain from any cannulation attempt and hand the endoscope over to a more experienced endoscopist from the very start, so as not to jeopardize further cannulation success. Perhaps during initial ERCP training focus should be shifted from bile

duct cannulation attempts by the trainee, leaving that to the trainer, and instead focusing on other technical skills to complete a successful ERCP, not putting the patient at increased risk for failed cannulation. Simulator training, training on models or only starting procedures on patients who have previously been sphincterotomized is a safer path in the early phase of ERCP-learning[22].

In previous studies it was found that the factor "trainee participation" might have a slight negative influence on bile duct cannulation[23,24]. No definitive explanation for this finding was shown, but trauma to the papilla was discussed as a possible explanation. In contrast, other studies have not been able to identify this problem when evaluating trainees learning ERCP[25,26]. Frost et al.[27] made a structured effort to answer this question. However, in contrast to the present study they could not find any negative impact of letting a trainee start cannulation. None of these studies[25–27] have, on the other hand, considered the impact of the endoscopic appearance of the papilla on cannulation difficulties. The present study was not designed to investigate this

unexpected finding, and consequently it needs to be evaluated in a more dedicated study to make any definitive statements regarding this finding. The same holds true for the post-ERCP pancreatitis (PEP) frequencies for the different papilla types. No significant differences between the papilla types regarding PEP frequency was seen in the present study, although there is a tendency that small papillae have a frequency of PEP in parallel with the increased frequency of difficult cannulation. In the present study, as well as in previous studies, there is a higher frequency of PEP if cannulation is difficult.[28,29] The definition for difficult cannulation used is constructed with the risk of PEP as a decisive factor[15].

When a new classification is made, to be used in a clinical setting, one has to make some kind of compromise between usefulness and precision. Previously there have been suggestions for a classification of the endoscopic appearance of the papilla but it has not undergone any interobserver validation and been applied in studies concerning pre-cut cannulation technique[9,30], not difficult cannulation per se. In the present study, we aimed at implementing a more universal, easy-to-use classification, in an everyday clinical setting to make the

results more generalizable. As in all studies where different observers are called upon to make a judgement and determine what they believe is the correct classification, there will always be an uncertainty as to whether the "correct" decision is made. In contrast, one could ask oneself, how useful, in the clinical situation, is a classification if only dedicated experts can determine the "correct" answer? In the present and our previous study, we have tried to balance these opposing aspects to make a classification that is easy to use and understand, but still interobserver-validated to a substantial degree, to both experts and beginners, making it relevant in everyday clinical practice.

To summarize and conclude, the present study has shown that the endoscopic appearance of the major duodenal papilla affects bile duct cannulation. Small, Type 2 and protruding or pendulous Type 3 papillae are more often difficult to cannulate, especially for inexperienced endoscopists. Furthermore, the finding that when a fellow endoscopists start attempting bile duct cannulation the frequency of failed cannulation rises, even when a more experienced endoscopist continues cannulation, raises some concerns regarding endoscopy training.

These findings have to be taken into consideration when performing studies regarding bile duct cannulation and in the training of future generations of endoscopists.

Table 1. Patient characteristics	
No of patients (n)	1401
Female	52%
Age, years, mean (SD)	66 (16)
Indication for ERCP	
Common bile duct stones	44%
Periampullary tumor	15%
Jaundice	13%
Stricture	9%
Primary sclerosing cholangitis	7%
Bile Leak	4%
Other	8%

Table 2. Frequency of difficult cannulation, depending on experience and papilla type

Experience / Papilla type	Expert	Intermediate	Fellow
Type 1, regular papilla	25%	45%*	66%*
Type 2, small papilla	43%	49%⊕	83%*
Type 3, protruding or pendulous papilla	36%	63%*	69%*
Type 4, creased or ridged papilla	32%	44%⊕	73%*
Overall	**30%**	**49%***	**69%***

*Significant difference ($p<0.05$) compared to Expert, ⊕ non-significant compared to Expert

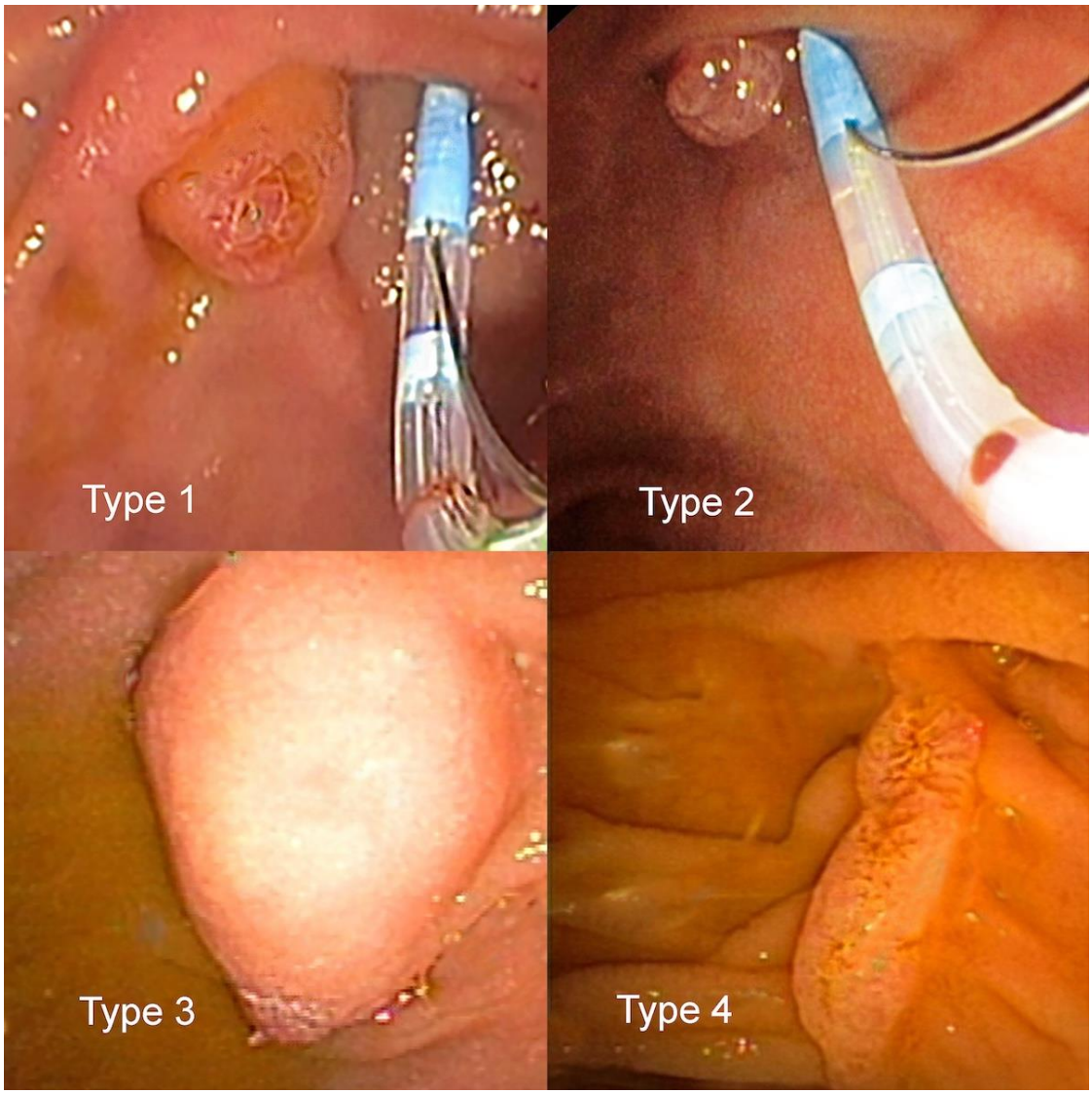

Figure 1. Classification of the endoscopic appearance of the papilla of Vater.

Type 1 "Regular papilla"- Most common type with no distinctive features "classic appearance"

Type 2 "Small papilla"- Small, often flat with a diameter not bigger than 3 mm (approx. 2 sphincterotome diam.)

Type 3 "Protruding or pendulous papilla"- A papilla that is protruding or bulging into the duodenal lumen sometimes hanging down, pendulous with the orifice oriented caudally

Type 4 "Creased or ridged papilla"- The ductal mucosa seems to extend distally out of the orifice either on a ridge or in a crease

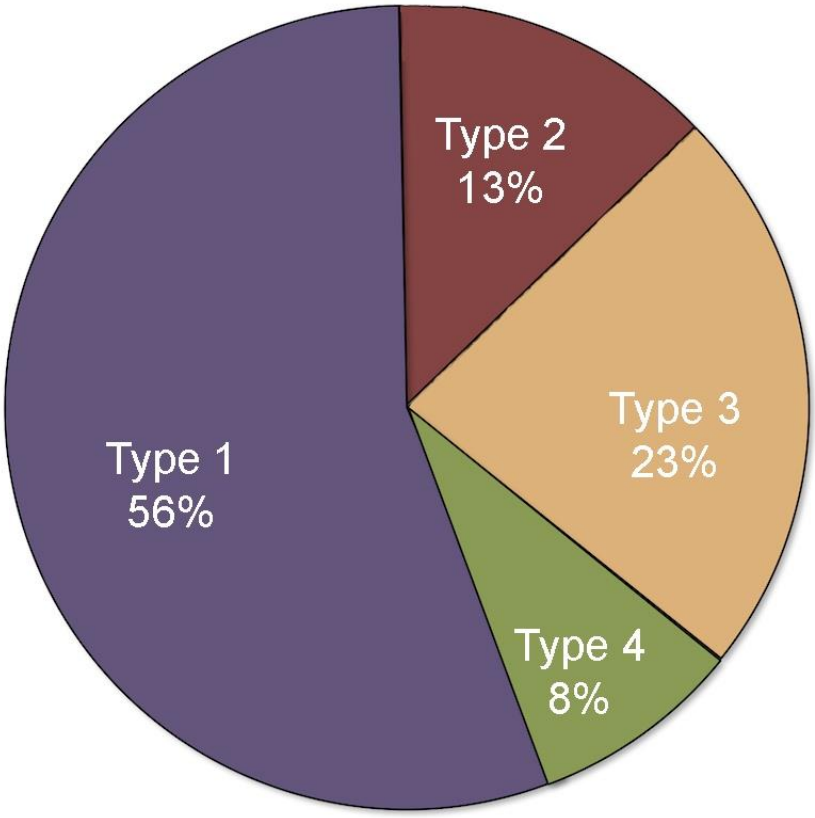

Figure 2. Distribution of the different papilla types

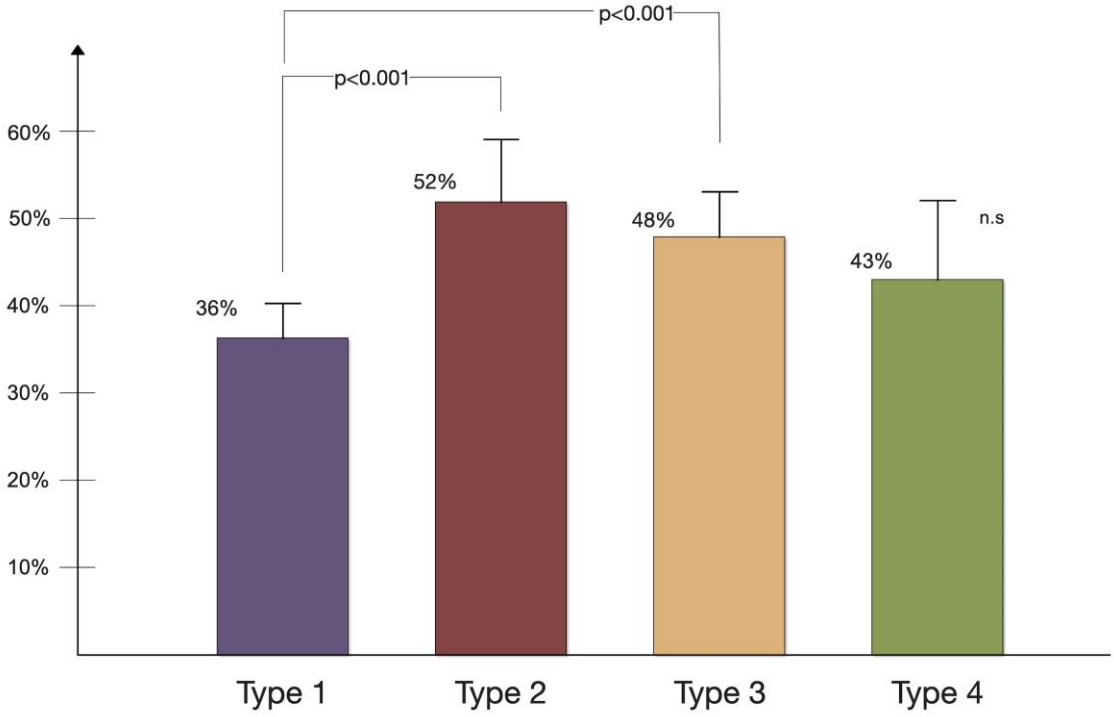

Figure 3. Frequency of difficult cannulation distributed among the different papilla types (95%CI)

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