Different interventions and a novel treatment of benign biliary strictures

Ph.D. Thesis

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1. INTRODUCTION

Benign biliary stricture is a rare condition, which could be successfully treated with collaboration of different clinical specialities (surgery, gastroenterology, radiology). There is no consensus concerning its best therapy in current clinical practice. The existing surgical and endoscopic solutions are effective, but still have a relatively high re-occlusion rate. Thus, the need to develop a therapeutic solution that will be successfull in this benign desease in the long term and put as low-burden as possible for patients.

2. OBJECTIVES

Our goal was to evaluate and compare the effectiveness of the existing therapies and work out a novel treatment which could be effective in the targeted treatment of benign biliary strictures in the future so it could improve the outcome and the long-term success rate for our patients.

2.1. Comparison of the available treatment options in benign biliary stricture- meta-analysis

- 2.1.1. Choosing_ the most effective method in benign biliary stricture treatment according to the literature
- 2.1.2. Comparison of the treatment's long-term success rate

- 2.1.3. Is there any inadequate terapeutic modalities in between the current treatments

2.2. The novel percutaneous therapy, pilot study

- 2.2.1. Work out a novel terapeutic strategy
- 2.2.2. Comparison of the patient's data and results in a pilot study
- 2.2.3. Evaluate the success of the therapy and drawing conclusions about its justification

3. METHODS

3.1. META-ANALYSIS

3.1.1. Materials

All published journal articles, which were related to benign biliary stricture were researched in three main electronic databases (PubMed, Embase és Cochrane Libary). We excluded languages other than English. Based on the accelerated development of various endobiliary stents we decided to exclude publications about endoscopy before 2000. At the other therapeutic modalities there was no publication date restriction. The selection of the publications was performed manually.

3.1.2. Inclusion criteria

Benign strictures were included only. The disease types were chronic pancreatitis, postoperative stricture and iatrogenic

trauma. All three treatments were included: surgery, endoscopic and percutaneous intervention. We evaluated all types of stents and their use: single plastic stent, multiple plastic stent, metal stent and fully covered metal stent. The surgical methods were choledochoduodenostomy, choledochojejunostomy, hepatoduodenostomy and hepaticojejunostomy. Both retrospective and prospective studies were accepted. Only publications with at least one-year follow-up after the close of the intervention according every single patient (definitive removal of stent) were included.

3.1.3. Exclusion criteria

All studies were excluded where the follow-up after the close of the interventional period were shorter than one year. To accurately evaluate the studies just full texts were accepted. We were not evaluated strictures related to transplantation becauseof the special surgical technique and therapy.

3.1.4. Statistical Analysis

All meta-analysis were performed with random effect model using the Der Simonian and Laird method. Q-statistics and I^2 indicator were calculated in each case to assess heterogenity. During the analysis we realized that the follow up times reported by the authors varied in a very wide range, even within

the same study. The biggest challenge of this work was to handle this difficulty and investigate whether the results effect the final conclusion. We used an alternative weighting method as well along with the conventional random effect weighting procedure: we multiplied the sample sizes with the (mean or median) follow up years thus allowing the follow up time to contribute to the weights. Bigger sample size results in smaller standard error which yields a bigger weight to the specific study and it allows us to see how the result change if we take into account this information in the weights. Comparing the results of the conventional weighting (Figure 1-2) and the one altered by the follow up time (Figure 3-4), the conclusions are robust concerning this difference. The two weighting methods yields almost exactly the same estimates and therefore do not affect the conclusion of the analysis.

3.2. THE NOVEL PRECUTANEOUS THERAPY, PILOT STUDY

3.2.1. Details of therapy

Each treatment started with a cholangiography to determine the obstruction level with the previously inserted transhepatic drain (biliary manipulation catheter ø10,2Fr lenght: 35cm). ***(Figure 5.A.)*** Then 40 mg (1 ml) triamcinolone (Kenalog, KRKA d.d.) was injected into the stricture at different directions with road

mapping technique. Based on the idea, we used a device that was designed by our team. It is a transluminal needle combined with a biliary manipulation catheter, so we could inject under sufficient resistance and perform a precise therapy due its flexible tip. ***(Figure 5.B.)*** After the injection, balloon dilatation (14 mm in diameter) with 5-bar pressure was made. ***(Figure 5.C.)*** Finally, a 10.2 Fr drain (biliary drain catheter ø10,2Fr, lenght 35cm) was left behind bridging the stricture. ***(Figure 5.D.)***

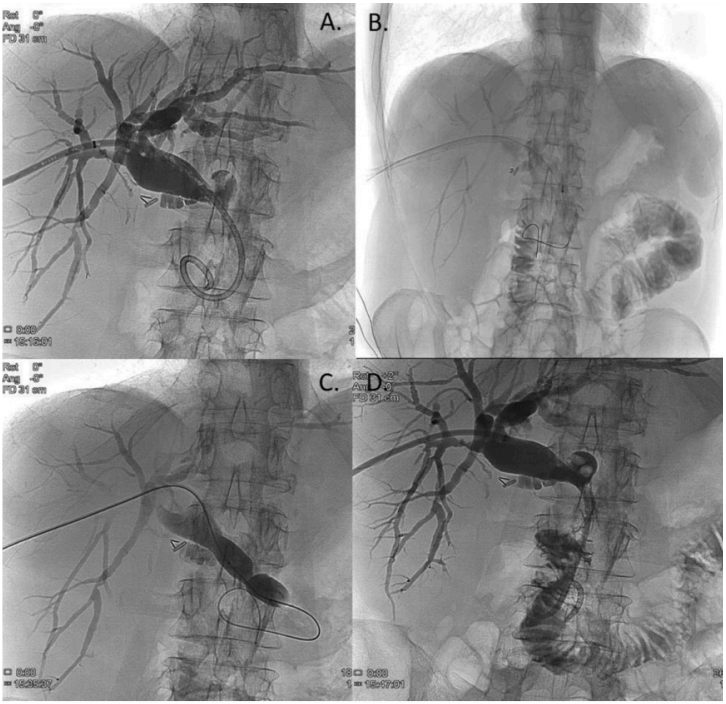

Figure 5. A. cholangiography, B. injection, C. balloon dilatation, D. drainage

This procedure was performed two more times with a one-month recovery period between treatments. The drains were removed two weeks after the third treatment and the cholangiographic data was recorded.

3.2.2. Patient selection

Inclusion criteria

Those patients were included in the study whom were over 18 years of age with a diagnosis of benign biliary stricture, and where the available therapeutic options (surgery, endoscopy) were contraidicated or not feasible, so according to the protocol the percutaneous intervention could be an option. No maximum age was specified at the time of selection, the inclusion criteria were met for both men and women (no gender specificity was applied).

4. RESULTS

4.1. META-ANALYSIS

4.1.1. Characteristics of the included studies

According to the inclusion and exclusion criteria a total of 24 articles were included in the present meta-analysis. One of the articles contained two groups, which were calculated individually. 14 publications of them were retrospective cohort studies, 11 were prospective trials, one of them contained both

retrospective and prospective results. No randomized controlled study was found.

4.1.2. Subgroup analysis of modified long term success rate

Six studies reported the long term disease free survival of surgical intervention. As shown in **Figure 1.**, the weighted mean of the surgical group was (ES 0,84; 95% CI [0,76; 0,93]). Within the endoscopically treated group, the weighted long term success rate of 3 studies with single plastic stent insertion was (ES 0,23; 95% CI [-0,01; 0,46]), 5 studies with multiple plastic stent insertion was (ES 0,79; 95% CI [0,69; 0,89]) and 5 studies with covered metal stent was (ES 0,76; 95% CI [0,62; 0,89]). The pooled mean value of percutaneous transhepatic drainage proved to be (ES 0,81; 95% CI [0,71; 0,90]). These data do not differ significantly from data with follow-up weighting discussed previously. **(Figure 3)**

Comparing the data of different groups by subgroup analysis shows no significant difference between surgical intervention, percutaneous transhepatic intervention and endoscopic multiple plastic stent or covered metal stent insertion (surgery vs. covered metal stent p = 0,19; surgery vs. multiple plastic stent p = 0,335; PTD—covered metal stent p = 0,342). However single plastic stent insertion indicates significantly worse long term disease free survival compared any other therapeutic

modalities (covered metal stent—single plastic stent p = 0,001; multiple plastic stent—single plastic stent p< 0,001; PTD—single plastic stent p< 0,001; surgery—single plastic stent p< 0,001).

4.1.3. Subgroup analysis of originally published long term success rate

Calculating with the previously presented subgroups we compared the long term success rate of different groups originally published in the publications but no difference was detected surgery—ES 0,84; 95% CI [0,75; 0,93], single plastic stent insertion—ES 0,23; 95% CI [-0,01; 0,46], multiple plastic stent insertion—ES 0,79; 95% CI [0,69; 0,89], covered metal stent insertion—ES 0,75; 95% CI [0,65; 0,85], percutaneous transhepatic intervention—(ES 0,75; 95% CI [0,66; 0,84]). **(Figure 2.)** These data do not differ significantly from data with follow-up weighting discussed previously. **(Figure 4.)**

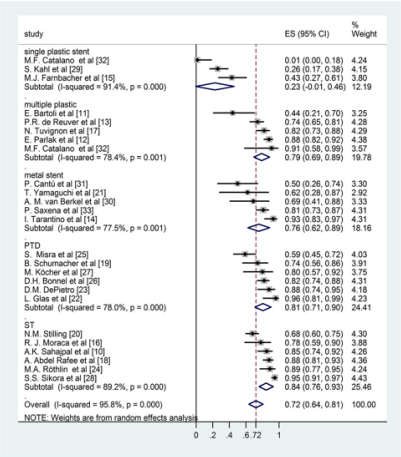

Figure 1. Forest plot comparing long term stricture resolution in different subgroups using modified rate with ordinary weighting.

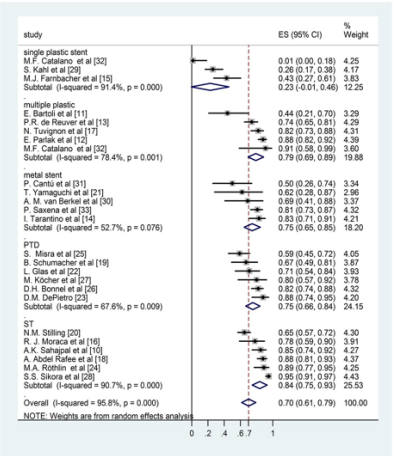

Figure 2. Forest plot comparing long term stricture resolution in different subgroups using originally published rate with ordinary weighting.

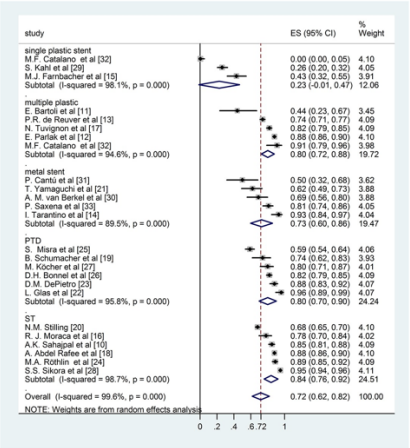

Figure 3. Forest plot comparing long term stricture resolution in different subgroups using modified rate with follow-up weighting.

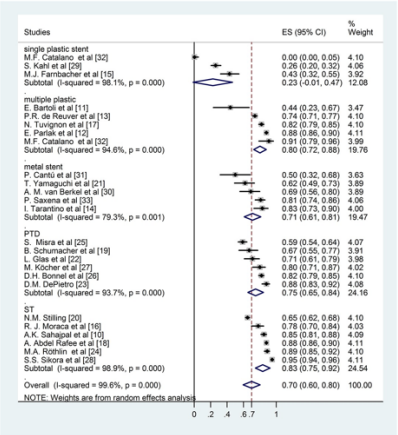

Figure 4. Forest plot comparing long term stricture resolution in different subgroups using originally published rate with follow-up weighting.

4.2. THE NOVEL PERCUTANEOUS THERAPY, PILOT STUDY

We successfully developed a method which is a relatively quick procedure (1-1,5 hour), does not put a heavy burden on the patient and it is easy to perform and repeat. The method requires co-operation from the patient, as it has to be repeated three times with a one-month omission. Additionally, during this period of time and for another two weeks after the last treatment a drain must be worn. The device with which the treatment was performed is easy to reproduce and it is easy to apply correctly. It enablesthe user to easily target the stricture and the manipulation catheter gives a sufficient resistance. The Hungarian Medical Research Council gave its approval to the device and to the treatment (062350/2015/OTIG). This single-center pilot study, conducted between February 2014 and June 2016, involved five patients (4 men, 1 woman) with mean age of 58.2 years (range 32-74). The clinical characterestics are shown in Table 1. **(Table 1.)**

Demographic and clinical data of patients					
AGE	*ETIOLOGY*	*ASA SCORE*	*PREVIOUS SURGERY*	*PREVIOUS ERCP*	*BILE DUCT STONE*
M	CP	II	FREY'S PROCEDURE	YES*	YES
F	LCL	III	HEPATICO-JEJUNOSTOMY	NO**	YES
M	LCL	II	HEPATICO-JEJUNOSTOMY	NO***	NO
M	CP	III	FREY'S PROCEDURE	YES****	YES
M	CP	III	FREY'S PROCEDURE	NO	YES

1.Table Clinical data of patient's age, gender, ethiology and past history. (F: female, M: male, CP: chronic pancreatitis, LCL: laparoscopic cholecystectomy laesion, ASA: American Society of Anesthesiology, ERCP: endoscopic retrograde cholangiography)

* failed stent implantation

** failed balloon dilatation

*** insufficient and narrow anastomosis

**** without long-term success

4.2.1. Results of the treatment

A total of 16 successful treatments were performed in 5 patients. The procedure resulted with a good radio-morphological results in all patients, which can be inferred

from the morphology of the bile duct anatomy that appears when the balloon is inflated. **(Figure 6.)**

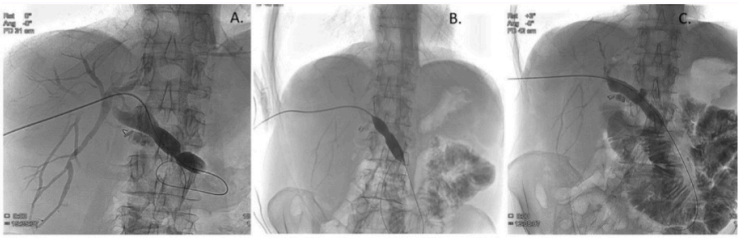

Figure 6. A. Balloon dilatation at the first, B. second, C. and third treatment.

During and after the treatment no side effects occured and there were no local or systemic side effects associated with triamcinolone. One minor complication (cholangitis) was detected, which is a known complication due to the nature of the disease and the intervention, and as such was not associated with the treatment. 4 patients had successful stone extraction (2 percutaneously assisted, 2 rendezvous technique). One patient required a repeated procedure due recurrent biliary stones one year after the final treatment. There were no recurrent stricture during the repeated percutaneous transhepatic cholangiograpy, the stone was passaged into the duodenum. (Table 2.)

RESULTS OF THE TREATMENT				
PATIENT #	*SIDE-EFFECT*	*MINOR COMPLICATION*	*MAJOR COMPLICATION*	*TREATMENT OF BILE STONES*
PATIENT 1	0	0	0	PERCUTANEOUS STONE EXTRACTION
PATIENT 2	0	0	0	PERCUTANEOUS STONE EXTRACTION
PATIENT 3	0	0	0	0
PATIENT 4	0	1*	0	ENDOSCOPIC STONE EXTRACTION
PATIENT 5	0	0	0	ENDOSCOPIC STONE EXTRACTION

Table 2.**: Results of the treatment**

***cholangitis**

Each intervention lasted on average 30-45 minutes. The inpatient length of stay averaged three days. The median follow-up period was 30.24 months (range 14.5-44.6 months). The first patient died of a treatment-unrelated cause (heart attack) 14.5 months after the end of treatment and he was excluded from the disease-free calculation. None of the patients had re-occlusion. The disease-free survival was 34.175 months as it previously mentioned.

5. CONCLUSIONS

- 5.1. Until now, there was no established procedure for the treatment of benign biliary stricture that provides good long-term success rate. According to our meta-analysis, surgery is considered to be the most effective method in the long term.
- 5.2. According to our meta-analysis surgery showed in the highest long term stricture resolution rate with 84 %, followed by multiple plastic stent insertion with 79 %, the percutaneous transhepatic treatment and the covered SEMS with 75 %, although the difference was not significant.
- 5.3. According to our meta-analysis the use of single plastic stent is not recommended.
- 5.4. We successfully developed a novel treatment and no complications were detected during or after the procedure, nor were any local or systemic side effects associated with triamcinolone. One minor complication (cholangitis) was detected, which is a known complication due to the nature of the disease and the intervention, and as such was not associated with the treatment.
- 5.5. the average intervention period during the pilot study were 30-45 minutes. The inpatient length of stay averaged three days. The median follow-up period was 30.24 months (range 14.5-44.6 months). The disease-free survival was

34.175 months, which was calculated after excluding the first patient who died 14,5 months after the last treatment due an unrelated cause.

- 5.6. Based on the results of the pilot study, the first percutaneous transhepatic corticosteroid injection with balloon dilatation is a successful alternative for the treatment of benign biliary stricture. Further prospective randomized sutdies are needed to prove this.

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