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Original Article

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Reproducibility of preoperative endoscopic injection of botulinum toxin into the sphincter of Oddi to prevent postoperative pancreatic fistula

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Abstract

Background: A postoperative pancreatic fistula (POPF) is the most common and potentially life-threatening surgical complication in pancreatic surgery. One possible pharmacological treatment could be the endoscopic injection of botulinum toxin (BTX) into the sphincter of Oddi to prevent POPF. Promising data reported a significantly reduced rate of clinically relevant POPF. We analyzed the effect of BTX injection in our patients undergoing distal pancreatectomy (DP).

Methods: A retrospective analysis of patients undergoing DP was performed. Patients with preoperative endoscopic injection of BTX into the sphincter of Oddi were included. The end points were postoperative outcomes including POPF. BTX patients were compared with a historical cohort and matched in a 1:1 ratio using a propensity score analysis.

Results: A total of 19 patients were treated with endoscopic injection of BTX before open (n = 8) or laparoscopic (n = 11) DP. The median age of the patients was 67 years and the mean body mass index was 25.9 kg/m². In median, the intervention was performed 1 day (range, 0–14 days) before the operation. There were no intervention-related complications. The incidence of POPF was not statistically different between the two groups: a clinically relevant POPF grade (B/C) occurred in 32% (BTX) and 42% (control; p = 0.737). Likewise, there were no significant differences in postoperative drain fluid amylase levels, morbidity, and mortality.

Conclusion: The present study could not reproduce the published results of a significant lowering of grade B/C POPF. The explanations could be the timing of BTX injection before surgery and the endoscopic technique of BTX injection. However, the conflicting results after BTX injection in two high-volume centers prompt a randomized controlled multicenter trial with trained endoscopists.

Keywords: botulinum toxin injection; distal pancreatectomy; postoperative pancreatic fistula.

Introduction

Distal pancreatectomy (DP) for benign or malignant diseases of the pancreatic body and tail is a standard procedure in gastrointestinal surgery. In comparison to pancreatoduodenectomy, DP is easier and less prone to complications, as a reconstruction of the pancreaticobiliary system or the digestive tract is not necessary in most cases. However, leakage from the pancreatic stump, resulting in a postoperative pancreatic fistula (POPF), is still a frequent and potentially life-threatening complication. The rate of POPF – according to the International Study Group of Pancreatic Surgery (ISGSP) [1, 2] – has been reported to reach 60% [3], and clinically relevant POPF (grades B/C) account for the majority of the overall rate of fistulas [4]. Despite various attempts to reduce the POPF rate, neither variations in the techniques of parenchymal transection [4, 5] nor additional measures such as a stump closure using a falciform ligament patch [6] or staple line reinforcement [7, 8] have significantly reduced the POPF rate. In some studies, endoscopic pancreatic
stenting was effective in the prevention of POPF [9–11]. However, a prospective single-center randomized controlled trial (RCT) in Sweden failed to show a prophylactic effect of pancreatic stent insertion in order to lower the POPF incidence [12]. To date, level I evidence from multicenter RCTs is lacking, although lowering of POPF is clinically relevant. The serious event of a POPF doubles the risk of death and may prolong the hospital stay with resultant increased costs and morbidity [13, 14]. Therefore, innovative and effective strategies are needed for the prevention of POPF.

One possible pharmacological treatment could be the endoscopic injection of botulinum toxin (BTX) A into the sphincter of Oddi [15]. BTX induces muscle relaxation and has been used as a safe and effective treatment option in patients with sphincter of Oddi dysfunction. Recently, Hackert et al. [16] reported a significantly reduced pancreatic fistula rate after DP by means of sphincter of Oddi BTX injection. No clinically relevant fistulas (grades B and C) were observed in these prospective phases I/II, which included 24 patients. To date, the administration of BTX for relaxation of the sphincter of Oddi is an off-label use. Because of the promising data, preoperative BTX injection was offered to patients scheduled for DP who consented to the off-label use in our department. The aim of this present study was to retrospectively review and analyze the effect of BTX injection on the prevention of POPF using a matched case study design. The primary end point was the occurrence of POPF according to the current ISGAPS definition within 30 days after DP. Further end points comprised the duration of total hospital stay, readmission, overall morbidity, and mortality.

Materials and methods

Data collection

Patients who underwent DP in our department from September 2012 to May 2017 were included for analysis. Preoperative BTX injection into the sphincter of Oddi was offered to patients from March 2012 to May 2017. Patients were informed about the off-label use and written consent was obtained. All patients who were offered the prophylactic BTX injection agreed and consented to this intervention. In total, 19 patients were treated with preoperative BTX (BTX subgroup). To compare the POPF rates and outcomes of these patients with preoperative injection of BTX into the sphincter of Oddi, a historical cohort of patients who had undergone DP within the study inclusion period was identified from a prospective pancreas database. After exclusion of patients who had undergone DP during multivisceral surgery for a primary lesion elsewhere other than in the pancreas, 67 patients without BTX injection before DP were identified. These patients were matched in a 1:1 ratio with the patients in the BTX subgroup, using a propensity score matching algorithm for the following variables: sex, age, body mass index (BMI), diagnosis (categorized), and surgical technique (laparoscopic versus open DP).

Technique of botulinum injection and DP

An esophagogastroduodenoscopy was performed for endoscopic identification of the papilla of Vater. A single, 1-mL suspension of 100 units of BTX (BOTOX®; Allergan, Pharmaceuticals Ireland, Westport, County Mayo, Ireland) reconstituted in 1 mL of 0.9% NaCl was injected into the sphincter of Oddi. Post-interventional patients were closely monitored, including clinical and laboratory parameters, to recognize possible complications associated with endoscopic instrumentation of the sphincter of Oddi [17]. DP was performed either in an open or laparoscopic fashion. Briefly, the first steps were mobilization of the left colon flexure to expose Gerota’s fascia and identification of the splenic artery and vein. The pancreas was transected using an endoscopic stapling device or a scalpel, with subsequent suture closure. If the pancreatic duct was identified, it was separately closed using Prolene 4-0. Lymphadenectomy and splenectomy were performed for malignant lesions according to consensus recommendations [18]. Abdominal drains were routinely placed near the pancreatic stump at the end of the operation.

Definition and grading of complications

POPF was defined as a drain fluid amylase concentration greater than three times the serum amylase levels, according to the ISGPS definition, on the third postoperative day [1]. Postoperative outcomes and complications were recorded, and complications were graded according to the Clavien-Dindo classification system [19].

Statistical analysis

Data analysis was performed using R-software statistics (R version 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria). The MatchIt package was used for propensity score matching of the patients. The Fisher exact test or the Welch two-sample t-test was used for comparison of categorical or quantitative variables. All tests were two-sided and considered significant at p < 0.05.

Ethical considerations

All patient-related data were obtained from an established database. Data were retrospectively analyzed using anonymized datasets of patients who underwent DP during the inclusion period of the study. The retrospective study was approved by the local institutional review board (decision no. 319082017).
Results

Patient characteristics and demographics

A total of 19 patients (10 male and 9 female) were treated with endoscopic injection of BTX into the sphincter of Oddi before DP. In median, the endoscopic injection was performed 1 day before the DP (range, 0–14 days) in an inpatient setting. The intervention was well tolerated by all included patients and there were no intervention-related complications, including post-interventional pancreatitis or bleeding. The median age of the BTX subgroup of patients was 67 years and the mean BMI was 25.9 kg/m². The most frequent indications for DP were pancreatic ductal adenocarcinoma, cystic tumors, or renal cell carcinoma metastases. Laparoscopic resection was performed in 11 cases. Pertinent patient demographic, pathological, and surgical characteristics were matched with historical controls, and thus did not differ significantly between the subgroups (Table 1).

Operative outcomes

In the total cohort of 38 patients, pancreatic transection was performed predominantly by linear stapling (n = 35). In 11 cases, the stapler line was additionally secured with sutures. The pancreatic remnant was further covered with a falciform ligament patch in 17 cases (nine cases in the BTX group versus eight cases in the control group). Splenectomy was performed in 14 patients (73.6 %) in the BTX group and in 11 patients (57.9 %) in the control group (p = 0.495).

The median operative times in the BTX group and the control group were 222 and 188 min, respectively (p = 0.325).

Table 1: Patient demographics and operative characteristics.

| Variable                        | BTX group (n = 19) | Control (n = 19) | p-Value |
|---------------------------------|--------------------|-----------------|---------|
| Sex, male/female (%)           | 10/9 (53%/47%)     | 7/12 (37%/63%)  | 0.515   |
| Age (years; IQR)               | 67 (60–75)         | 70 (63–78)      | 0.377   |
| BMI (kg/m²)                    | 25.9 (23.2–28.6)   | 27.1 (23.2–29.4)| 0.678   |
| ASA score (I–III)              | 9/10               | 12/7            | 0.515   |
| Histopathology                 |                    |                 |         |
| PDAC                            | 6                  | 4               | 0.714   |
| Cystic tumor                    | 5                  | 10              | 0.184   |
| RCC                             | 4                  | 3               | 0.184   |
| Others                          | 4                  | 2               | 0.660   |
| Operative technique             |                    |                 |         |
| Lap/open                        | 11/8               | 12/7            | 1.000   |
| Stapler/scalpel                 | 19/0               | 16/3            | 0.230   |
| Patch/no patch                  | 9/10               | 8/11            | 1.000   |
| Splenectomy: yes/no             | 14/5               | 11/8            | 0.495   |
| Cholecystectomy: yes/no         | 3/16               | 4/15            | 1.000   |
| Operation time (min)            | 222 (160–272)      | 188 (133–235)   | 0.325   |
| Blood loss (mL)                 | 200 (100–300)      | 100 (100–300)   | 0.559   |
| POPF, n (%)                     |                    |                 |         |
| BL                              | 6 (31.6%)          | 3 (15.8%)       | 0.447   |
| Grade B/C                       | 6 (31.6%)          | 8 (42.1%)       | 0.737   |
| CT drain                        | 2 (10.5%)          | 4 (21.1%)       | 0.660   |
| Hospital stay (days)            | 11 (10–17)         | 12 (10–18)      | 0.400   |
| Readmission: yes/no             | 1/18               | 4/15            | 0.340   |
| Morbidity (>grade II)b          | 3 (15.8%)          | 4/19 (21.1%)    | 1.000   |
| Mortality                       | 0 (0%)             | 1 (5.3%)        | 1.000   |

Data are presented as absolute numbers (and %, if indicated) for categorical variables, or as median plus interquartile range for quantitative variables. ASA, American Society of Anesthesiologists; BL, biochemical leak; BTX, botulinum toxin A; CT, computed tomography; IQR, interquartile range; Lap, laparoscopic; Patch, creation of a falciform ligament patch to cover the pancreatic remnant; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula; RCC, renal cell carcinoma. *Extended resection including cholecystectomy or other organs. †Postoperative morbidity was graded according to the Clavien-Dindo classification.
Most importantly, the primary end point of the study (incidence of POPF) was not statistically different between the two groups (Table 1). A clinically relevant POPF grade (B or C) occurred in 32% (BTX) and 42% (control; p = 0.737). An interventional, computed tomography (CT)-guided, drainage during the postoperative course was necessary in two patients (10.5%, BTX) and in four patients (21.1%, control), respectively. Likewise, the drain amylase levels on postoperative day 3 were not significantly different between the groups (p = 0.954). In the BTX group, the median amylase was 10.1 μmol/s*L [interquartile range (IQR) 2.9–28.0] (normal serum level defined as <0.88 μmol/s*L), compared with 5.0 μmol/s*L (2.6–31.8) in the control group (Figure 1).

The postoperative morbidity was assessed using the Clavien-Dindo classification. Complications requiring interventional or operative treatment or causing life-threatening conditions (>grade II) were observed in three (15.8%, BTX) and four (21.1%, control) patients, respectively (p = 1.000). One patient died during the postoperative course (2.6%). This patient was planned for discharge from the hospital and died unexpectedly due to an acute thrombosis of the inferior vena cava.

**Hospital stay and readmission**

Hospital stay was comparable in the two groups with an IQR between 10 and 18 days. We observed one readmission in the BTX group (1/19; 5.6%), compared with four patients (21.5%) in the control group.

**Discussion**

The development of a POPF is the most common and potentially life-threatening surgical complication in pancreatic surgery. Despite technical advances in the perioperative setting, the incidence of POPF still represents a significant medical and economic problem. The revised consensus definition of POPF in the year 2016 underlined the relevance of grade B and C fistulas. Asymptomatic POPFs with no clinical consequence were therefore classified as only a biochemical leak [2]. Grades B and C POPFs are symptomatic fistulas that require interventional management (such as antibiotics and/or percutaneous drainage for grade B, or reoperation for grade C). Once a postoperative patient suffers from a grade B or C pancreatic fistula, a series of other severe complications can develop, leading to intra-abdominal infection, bleeding (“post-pancreatectomy hemorrhage”), and life-threatening shock.

Several risk factors for the development of POPF have been extensively evaluated. For example, patient-related factors, e.g. advanced age, increased BMI, a high American Society of Anesthesiologists score, or histological evidence of pancreatitis at the pancreatic remnant, increase the risk of POPF [20–25]. Surgery-related risk factors include a prolonged operation time [20, 23], excessive blood loss [26, 27], and the failure to specifically ligate the main pancreatic duct [24, 28]. Some studies have indicated that endoscopic pancreatic stenting was effective in the prevention of POPF after DP [28, 29]. Additional reports have shown that, in the case of a manifested POPF, the endoscopic insertion of a stent into the proximal pancreatic duct through the papilla can facilitate healing of the fistula [30].

Preoperative injection of the sphincter of Oddi using BTX offers an interesting pharmacological approach for sphincter relaxation without papillotomy or stent placement. The approach has gained additional attractiveness through a recent study, in which no clinically relevant
POPFs were diagnosed following BTX injection into the sphincter of Oddi [16]. However, the present study could not reproduce these promising results. Several possible explanations should be discussed.

Firstly, the timing of BTX injection before surgery could have been too short before DP. Hackert et al. [16] reported a median delay of 6 days (range, 0–10 days) before DP, whereas, in the present study, most of the patients underwent BTX injection 1 day before surgery. Of note, the optimal time point for BTX injection into the sphincter of Oddi is unclear. An immediate action of BTX is known from aesthetic or esophageal surgery [31, 32]. Additionally, there are reports on the use of intraoperative BTX injection into the pylorus muscle during esophagectomy aiming at a reduced rate of delayed gastric emptying [33]. A significant improvement of gastric emptying was observed on postoperative day 4 in the BTX subgroup. This result indicates a quick clinical effect in the pylorus after a few days. Other clinical data stem from a randomized study on BTX injection into the lower esophageal sphincter in patients with achalasia [34]. Here, a significant improvement in clinical symptoms was noted after 1 week, which was the earliest time point to monitor the symptom score. Most interestingly, BTX injection into the sphincter of Oddi in an experimental canine model significantly lowered the common bile duct pressure within 24 h and the effect continued for 14 days [35].

Together, these results from various smooth muscle sphincters of the upper gastrointestinal tract propose a clinically relevant sphincter relaxation after 1 day and a clinically measurable effect at least after 4–7 days. Although we do not know the most critical postoperative day for POPF development after DP, a BTX injection at least 24 h before surgery seems logical. In light of the present results and the published results by Hackert et al. [16], a delay of 4–7 days before surgery could still be a critical variable to improve the clinical effect of BTX-induced sphincter relaxation. With regard to the present results, there were only three patients in the BTX subgroup (n=19) who underwent BTX injection at a minimum of 5 days before pancreatectomy. One of the three patients had a POPF (grade B).

Secondly, the technique and efficacy of the endoscopic BTX injection has to be argued. In the present study, 100 units of BTX were injected directly into the papilla, with direct endoscopic visualization of the papilla during the injection ensuring the correct placement of the toxin. This is in line with the technique reported by the Heidelberg group [16]. In addition, all interventions were carried out by experienced gastroenterologists with long experience in endoscopic retrograde cholangiopancreatography techniques. Wehrmann et al. [15] described the needle being inserted into the upper margin of the papillary orifice at the 1 o’clock position for the administration of BTX. In our series, BTX was not administered at the 1 o’clock position in all cases, which might have affected the efficacy. It could also be argued that the presented failure of prophylactic BTX injection was because the BTX injection was not deep enough into the muscle of the sphincter.

Thirdly, the present study was not a prospectively controlled trial and included only a small cohort of 19 patients. Hence, the results should be interpreted with caution.

Nevertheless, the discrepant results after prophylactic BTX injection to prevent POPF after DP in two high-volume centers are of interest and relevant, because reproducibility is a key determinant and a requirement for a multicenter RCT evaluating preventive BTX injection. A significant reduction of clinically relevant POPF rates may only be achieved if BTX is injected in a perfect position and with an optimal delay before surgery. Measures to guarantee a comparable quality of endoscopic BTX injection could include a mandatory endoscopic training session (during which experienced endoscopists are trained specifically in the procedure of sphincter of Oddi injection and its pitfalls), or definition of the time of injection before surgery and definition of standardized locations and steps for the endoscopic procedure.

Moreover, an analog score of the fistula risk score (FRS), which has been developed by several authors for pancreateoduodenectomy [36, 37], could also be helpful for patient selection before DP. It might be an overtreatment if all patients were to undergo BTX injection before DP and were exposed to the possible complications of an additional endoscopic intervention. The assessment of this DP-FRS could enable us to select patients who would benefit from BTX injection.

In conclusion, the present data with conflicting results support a randomized controlled multicenter trial with trained endoscopists in order to assess the efficacy of prophylactic BTX injection into the sphincter of Oddi.

Author Statement
Research funding: Authors state no funding involved.
Conflict of interest: Authors state no conflict of interest. Informed consent: Patients were informed about the off-label use and written consent was obtained. Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies, was performed in accordance to the tenets of the Helsinki Declaration, and has been approved by the local institutional review board (decision no. 319082017).
Author Contributions
Andreas Volk: study design; data acquisition; data analysis; data interpretation; drafting of the manuscript. Marius Distler: study design; data interpretation; manuscript revision. Benjamin Müssle: study design; data interpretation; manuscript revision. Marco Berning: study design; data interpretation; manuscript revision. Jochen Hampe: study design; data interpretation; manuscript revision. Thilo Welsch: study design; data acquisition; data analysis; data interpretation; drafting of the manuscript.

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Supplemental Material: The article (https://doi.org/10.1515/iss-2017-0040) offers reviewer assessments as supplementary material.
Reviewer Assessment

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Reviewers’ Comments to Original Submission

Reviewer 1: anonymous

Nov 17, 2017

Reviewer Recommendation Term: Reject
Overall Reviewer Manuscript Rating: 60

Custom Review Questions Response
Is the subject area appropriate for you? 4
Does the title clearly reflect the paper’s content? 2
Does the abstract clearly reflect the paper’s content? 4
Do the keywords clearly reflect the paper’s content? 4
Does the introduction present the problem clearly? 4
Are the results/conclusions justified? 3
How comprehensive and up-to-date is the subject matter presented? 3
How adequate is the data presentation? 4
Are units and terminology used correctly? 4
Is the number of cases adequate? 1 - Low/No
Are the experimental methods/clinical studies adequate? 3
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 3
Please rate the practical significance. 2
Please rate the accuracy of methods. 3
Please rate the statistical evaluation and quality control. 3
Please rate the appropriateness of the figures and tables. 4
Please rate the appropriateness of the references. 4
Please evaluate the writing style and use of language. 4
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes
Comments to Authors:
Basically, this is an interesting subject raised by the authors with a relevant clinical connection. However, the limited number of cases, the design of the study (comparison with historical patient collective) and the inhomogeneity of the patient cohort treated with BTX-injection casts the investigation in a questionable light. For example: BTX-injection varies between 1 and 14 days before resection! Treatment of pancreatic resection margin varies widely and prevents comparability. This is reflected by the lack of clear and interpretable results.

Reviewer 2: Ernst Klar
Oct 30, 2017

Reviewer Recommendation Term: Revise with Major Modification
Overall Reviewer Manuscript Rating: 80

Custom Review Questions Rating: Response
Is the subject area appropriate for you? 4
Does the title clearly reflect the paper’s content? 4
Does the abstract clearly reflect the paper’s content? 4
Do the keywords clearly reflect the paper’s content? 4
Does the introduction present the problem clearly? 4
Are the results/conclusions justified? 3
How comprehensive and up-to-date is the subject matter presented? 3
How adequate is the data presentation? 3
Are units and terminology used correctly? 4
Is the number of cases adequate? 3
Are the experimental methods/clinical studies adequate? 4
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 4
Please rate the practical significance. 4
Please rate the accuracy of methods. 3
Please rate the statistical evaluation and quality control. 4
Please rate the appropriateness of the figures and tables. 4
Please rate the appropriateness of the references. 3
Please evaluate the writing style and use of language. 3
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
The current study was laid out to analyze the potential effect of Botulinum injection into the papilla of Vater on the formation of B and C pancreatic fistula and related clinical parameters following distal pancreatectomy. This is a retrospective analysis of 19 patients who gave informed consent to endoscopic Botulinum injection into the papilla of Vater. As control group 1:1 propensity score matching was performed from a total group of 67 patients without Botulinum injection. No difference could be detected between the groups regarding fistula formation, LOF and other endpoints.

Comments:
The technique of BTX injection should be described in more detail. Why was BTX not injected in the optimal location in most of the patients despite the fact that "experienced" gastroenterologists were involved.
Data collection:
It should be stated how many patients refused to take part in the study.
Range of injection 0-14 days preoperatively. This represents a wide range. Literature data on the optimal time point should be discussed.
Splenectomy was performed in 14 patients (73.6 %) in the BTX and in 11 patients (57.9 %) in the control group (p=0.495). The authors should explain the reason for this significant difference between the groups if this represents a matched pair analysis.
Discussion:
Timing of BTX injection. It should be made clearer that the authors imply 1 day preoperatively may be sufficient due the fast action of BTX shown in other applications (e.g. cosetics). Having this argument in mind, it is hard to understand that the later timepoint of injection preoperatively brought into discussion to explain the different result in the study by Hackert et al. In this study the median is 6 days (range 0-10 days) whereas it is 1 day in the current study (range 0-14 days). The authors should present a clearer line of arguments.
The authors propose to optimize the time of injection preoperatively in general. They should specify what they would recommend as potentially optimal time on the basis of literature data also in experimental settings.

As conclusion the authors propose a RCT with trained endoscopists. They should explain the difference between “experienced” endoscopists who were involved in their study and “trained” endoscopists as postulated.

Reviewer 3: Karl Oldhafer

Nov 30, 2017

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: 80

Custom Review Questions Response
Is the subject area appropriate for you? 5 - High/Yes
Does the title clearly reflect the paper’s content? 5 - High/Yes
Does the abstract clearly reflect the paper’s content? 4
Do the keywords clearly reflect the paper’s content? 4
Does the introduction present the problem clearly? 4
Are the results/conclusions justified? 2
How comprehensive and up-to-date is the subject matter presented? 4
How adequate is the data presentation? 4
Are units and terminology used correctly? 4
Is the number of cases adequate? 1 - Low/No
Are the experimental methods/clinical studies adequate? 3
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 4
Please rate the practical significance. 4
Please rate the accuracy of methods. 3
Please rate the statistical evaluation and quality control. 4
Please rate the appropriateness of the figures and tables. 3
Please rate the appropriateness of the references. 4
Please evaluate the writing style and use of language. 3
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
Interesting Topic
important clinical issue
good writing and good idea, however the number of patients is very small

Authors’ Response to Reviewer Comments

Dec 11, 2017

Point-by-point Response

Reviewer #1:
Basically, this is an interesting subject raised by the authors with a relevant clinical connection.
(A) However, the limited number of cases, the design of the study (comparison with historical patient collective) and
(B) the inhomogeneity of the patient cohort treated with BTX-injection casts the investigation in a questionable light. For example: BTX-injection varies between 1 and 14 days before resection!
(C) Treatment of pancreatic resection margin varies widely and prevents comparability. This is reflected by the lack of clear and interpretable results.
IV — Volk et al.: Botulinum toxin injection and distal pancreatectomy

DE GRYUTER

We thank the reviewer for his good remarks.

(A) We agree that our study comprises only a limited number of cases but so far there is only one comparable study by Hackert et al which includes 24 patients with distal pancreatectomies and BTX injection (Hackert et al. Surgery 2017, see reference nr.16), i.e. a comparable cohort size. We agree that a large randomized trial would be most desirable study method to gain sufficient evidence for BTX injection in the sphincter of Oddi. However, our off-label experience discovered important findings that should be considered when using the BTX injection or designing such a trial (timing of BTX injection, homogeneity of the groups). Therefore, we underlined the limits of the small cohort in our initial discussion (page 10).

(B) With regard to the optimal preoperative timing of BTX injection – which varied between 1 and 14 days before resection in our study – we learned that the exact time point is currently unknown and probably an important variable for the success of the intervention. In the study by Hackert, period between BTX injection and distal pancreatectomy also ranged from 0-10 days with a median of 6 days prior to distal pancreatectomy. The optimal timing of BTX injection is now extensively discussed in the revised version (Discussion, page 9-10).

(C) Again, we thank the reviewer for his concerns. There were 3 patients with conventional transection of the pancreas using the scalpel, and the difference between the groups was not significant. Moreover, the DISPACT trial showed, that there seems to be no relevant difference in POPF rate after either stapling closure or transection using the scalpel/hand-sewn stump during distal pancreatectomy (Diener et al. Lancet 2011; 377(9776):1514-22). We therefore believe, that it is unlikely that the 3 patients with hand-sewn pancreatic remnant significantly impact the outcome of preoperative BTX injection. Moreover, Hackert et al. observed no single clinical relevant POPF in their BTX trial, although 25% of the patients had a scalpel transection.

Reviewer #2:

1. The technique of BTX injection should be described in more detail. Why was BTX not injected in the optimal location in most of the patients despite the fact that “experienced” gastroenterologists were involved.

Thank you for this critical remark. The endoscopists who performed the BTX injection at our University center were all experienced with upper GI endoscopy and ERCP. The BTX injections were performed by four different endoscopists, and because of the anatomical location of the papilla, BTX was not injected at the preferred and previously described one o’clock position. Secondly, there is no immediate control monitoring whether the BTX was sufficiently injected into the sphincter muscle or not. Because our results did not confirm the positive effect observed by Hackert et al., we critically discussed the technique of BTX injection in the manuscript (page 10).

2. Data collection: It should be stated how many patients refused to take part in the study.

All patients who were offered the off-label BTX injection consented to this intervention. This information was added to the manuscript (page 5).

3. Range of injection 0-14 days preoperatively. This represents a wide range. Literature data on the optimal time point should be discussed.

We would like to discuss this remark together with item 5 (see below), since the two remarks aim at the same problem.

4. Splenectomy was performed in 14 patients (73.6%) in the BTX and in 11 patients (57.9%) in the control group (p=0.495). The authors should explain the reason for this significant difference between the groups if this represents a matched pair analysis.

As indicated in the Methods section (paragraph “Data collection”, page 5), the variable “simultaneous splenectomy” was not included in the propensity score matching algorithm. However, the difference of splenectomy was not significantly different between the two groups.

5. Discussion: Timing of BTX injection. It should be made clearer that the authors imply 1 day preoperatively may be sufficient due the fast action of BTX shown in other applications (e.g. cosmetics). Having this argument in mind, it is hard to understand that the later timepoint of injection preoperatively brought into discussion to explain the different result in the study by Hackert et al. In this study the median is 6 days (range 0-10 days) whereas it is 1 day in the current study (range 0-14 days). The authors should present a clearer line of arguments.

This is a very important comment. Our study might indicate that the timing of BTX injection is crucial. However, the optimal time point for BTX injection into the sphincter of Oddi is unclear. It is correct, that Hackert applied the injection at a median of 6 days before surgery, although the period ranged from 0-10 days. There are reports of the use of intraoperative BTX injection into the pylorus muscle during esophagectomy aiming at a reduced rate of delayed gastric emptying (Cerfolio et al. J Thoracic Cardiovasc Surg 2009). A significant improvement of gastric emptying was observed on postoperative day 4 in the BTX subgroup. This result indicates a quick clinical effect in the pylorus after a few days. Additional data stem from a randomized study on BTX injection into the lower esophageal sphincter in patients with achalasia (Pasricha et al. N Engl J Med 1995). Here, a significant improvement in clinical symptoms was noted after 1 week, which was the earliest time point to monitor the symptom score.

Most interestingly, experimental BTX injection into the sphincter of Oddi in a canine model significantly lowers the common bile duct pressure within 24 hours. This effect continued for 14 days (Marks et al. Am J Surg 2001).
Together, these results from other smooth muscle sphincters of the upper GI tract propose a clinical relevant sphincter relaxation after 1 day, and a clinically measurable effect at least after 4-7 days. Although, we do not know the most critical postoperative day for POPF development after distal pancreatectomy, a BTX injection at least 24 hours before surgery seems logical. In light of the present results and the published results by Hackert et al. a delay of 4-7 days before surgery could still be a critical variable to improve the clinical effect of BTX-induced sphincter relaxation. In our present study, there were only three patients in the BTX subgroup (n=19), who underwent BTX injection at a minimum of 5 days before pancreatectomy. Within these three patients, there was one POPF Grade B. These arguments are now further discussed in the revised manuscript (pages 9-10).

6. As conclusion the authors propose a RCT with trained endoscopists. They should explain the difference between “experienced” endoscopists who were involved in their study and “trained” endoscopists as postulated.

Thank you for your comment. “Experienced” endoscopists were considered to be endoscopists with a long-standing practice in general endoscopic interventions (including e.g. upper GI endoscopy, ERCP or endoscopic stent placement). On the other side, “trained” endoscopists should have completed a specific training of BTX injection into the sphincter Oddi by an instructor who has a significant experience with this specific intervention (e.g. >10 cases). This is now specified in the revised version of the manuscript (page 11).

Reviewer #3:

However the number of patients is very small.

We agree that our study comprises only a limited number of cases but so far there is only one comparable study by Hackert et al., which includes 24 patients with distal pancreatectomies after BTX injection. These numbers are almost comparable to our study. Please see also our comment to reviewer #1 (A).

Again the authors thank the reviewers for their helpful and valuable comments.

Reviewers’ Comments to Revision

Reviewer 2: Ernst Klar

Jan 02, 2018

| Reviewer Recommendation Term: | Accept |
|-------------------------------|--------|
| Overall Reviewer Manuscript Rating: | 66 |

| Custom Review Questions | Response |
|-------------------------|----------|
| Is the subject area appropriate for you? | 4 |
| Does the title clearly reflect the paper’s content? | 1 - Low/No |
| Does the abstract clearly reflect the paper’s content? | 4 |
| Do the keywords clearly reflect the paper’s content? | 3 |
| Does the introduction present the problem clearly? | 4 |
| Are the results/conclusions justified? | 4 |
| How comprehensive and up-to-date is the subject matter presented? | 4 |
| How adequate is the data presentation? | 4 |
| Are units and terminology used correctly? | 4 |
| Is the number of cases adequate? | 3 |
| Are the experimental methods/clinical studies adequate? | 3 |
| Is the length appropriate in relation to the content? | 4 |
| Does the reader get new insights from the article? | 4 |
| Please rate the practical significance. | 4 |
| Please rate the accuracy of methods. | 3 |
| Please rate the statistical evaluation and quality control. | 4 |
| Please rate the appropriateness of the figures and tables. | 3 |
| Please rate the appropriateness of the references. | 4 |
Please evaluate the writing style and use of language. 3
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
The main focus of the primary review was the adequate timing of botulinum injection. This has now been addressed properly by the authors.