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Perioperative hydrocortisone treatment reduces postoperative pancreatic fistula rate after open distal pancreatectomy. A randomized placebo-controlled trial

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ABSTRACT

Background: Postoperative pancreatic fistula (POPF) is the most common complication after distal pancreatectomy (DP). In a recent RCT on pancreaticoduodenectomy (PD), perioperative hydrocortisone (HC) treatment reduced Clavien-Dindo (C-D) III-V complications. The aim of this study was to investigate whether perioperative HC treatment reduces the overall complications and clinically significant POPF after distal pancreatectomy (DP).
Methods: Fourty consecutive patients undergoing DP were randomized to receive intravenous HC 100mg/placebo every eight hours until the second postoperative day. Thirty-one patients were completed with DP and received HC/placebo every 8 h for two days postoperatively. The primary endpoint was overall complications (C-D III-V) and the secondary endpoint was the development of clinically significant POPF.
Results: Pancreatic duct diameter, operative time and blood loss were similar in the groups. Ninety-day mortality was zero. With HC treatment the rates of C-D III-V complications tended to be lower compared to the placebo group (5.9% vs 21.4%, $p = 0.034$). The rate of grade B/C POPF was significantly reduced with HC treatment compared to the placebo group (5.9% vs. 42.9%, $p = 0.028$).
Conclusion: Perioperative HC treatment may have a favourable effect on overall major complications after open DP. HC treatment reduces the incidence of clinically significant POPF after open DP.
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Introduction

Post-operative pancreatic fistula (POPF) is the most common complication after DP, and the incidence remains high ranging 16–50% [1,2]. POPF is often associated with other complications, including wound infection, intra-abdominal abscess, delayed gastric emptying (DGE), postpancreatectomy haemorrhage (PPH), wound infection or sepsis [3,4]. Many surgical strategies have been studied to decrease fistula formation after DP [5–9] as well as endoscopic pancreatic duct decompression [10,11] and pharmaceutical measures [12].

We have shown in a recent RCT that perioperative hydrocortisone (HC) treatment reduces major complications (Clavien-Dindo III-V) after pancreaticoduodenectomy (PD) in high-risk patients with "soft", acinar-cell rich pancreas. HC treatment also tended to reduce the rate of clinically relevant POPF, but the difference was not statistically significant in this patient population alone (11% vs 27%; $p = 0.118$) [13].

The aim of this study was to investigate whether perioperative HC treatment reduces major complications (Clavien-Dindo III-V) and prevents the risk of POPF after open DP.

Methods

We conducted a prospective, single-centre, randomized trial at Tampere University Hospital, Finland. The RCT was conducted according to the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Tampere University Hospital. The study was designed simultaneously with another study on HC treatment in PD patients, reported recently in Annals of Surgery

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[13] and conducted partly parallel with this study. The Clinical Trial number is NCT01460615. The study was duly monitored and approved by the Finnish Medicines Agency (FIMEA).

Patients

Eligibility criteria included consecutive adult patients scheduled for elective, open DP for a disease of the pancreatic body or tail. Patients with ongoing cortisone treatment, ceftriaxone allergy or chronic pancreatitis were excluded. It was intented to include only patients with soft high-isk pancreas in the study. The patients gave their written and oral informed consent before randomization.

Randomization

The randomization list was made at the beginning of the study by a biostatistician. After providing written informed consent, patients were randomized before surgery to either the HC or the placebo group. The research nurse delivered the externally similar HC/placebo bags to the surgical ward on the morning of the procedure according to the randomization number. The HC solution contained hydrocortisone sodium succinate (Solu-Cortef; Pfizer Manufacturing, Puurs, Belgium) in 0.9% sodium chloride solution (Natriumklorid Braun, 9 mg/mL; B. Braun Melsungen, Melsungen, Germany) Infusion bags were filled with 100 mg hydrocortisone in 2 ml of sodium succinate added into 100 ml of 0.9% sodium chloride solution. The placebo solution was made up by adding 2 ml of 0.9% sodium chloride solution into 100 ml of 0.9% sodium chloride solution.

Intervention

All operations were open procedures with a standard technique performed by experienced surgeons. No laparoscopic procedures were included in the study to standardize the operation. No octreotide or pasireotide were used. Pancreatic parenchyma was divided with a scalpel. Bleeding was controlled with Prolene 5–0 (Ethicon, USA) suturing. During the operation the percentage of acini cells in the pancreatic transection line was analysed by the pathologist [14]. Pancreas texture type was also estimated to be either soft or hard. Pancreatic duct diameter was measured by probing. All patients underwent standard hand-sewn closure of the stump. The main pancreatic duct was closed separately by suturing, followed by oversewing of the pancreatic stump with interrupted 4-0 Maxon (Covidien, USA) sutures. A Penrose drain was placed beside the stump.

At the induction of anaesthesia, all patients received a routine antibiotic prophylaxis of ceftriaxone 2 g (Rocephalin; Roche, Basel, Switzerland) and metronidatzole 500 mg (Metronidatzole; Brown, Melsungen, Germany) intravenously and either HC 100 mg or placebo intravenously depending on the randomization. Patients needing other resections than DP were excluded from the study. The patients who continued in the study received HC 100 mg/placebo every eight hours until the second postoperative day (total of 9 doses). Ceftriaxone 2 g i.v. was also continued until the second postoperative day.

Postoperatively the patients were followed-up according to the standard pancreatic resection protocol of Tampere University Hospital. Abdominal drain output was measured and recorded daily. Amylase concentration was measured on the third postoperative day from the drain and repeatedly thereafter if the drain was still in place. The drain was removed when the amylase levels were less than three times the serum upper limit and the fluid was clear. Patients' age, sex, BMI and comorbidities were recorded. Postoperative complications; fistulas, bleeding, wound infections, general infections, abscesses and 90-day mortality were recorded prospectively and compared between the groups.

Endpoints and definitions

The primary endpoint was the development of overall complications and the secondary endpoint was the development of clinically relevant POPF. The study was conducted before the new ISGPF classification, and thus the original ISGPF classification was used for POPF grading in the analysis. Grade B and C POPF were defined as clinically significant POPFs [15]. The overall postoperative complications were graded by Clavien-Dindo scoring [16]. Overall morbidity was defined as Grades II-V, and major complications as Grades III-V according to the Clavien-Dindo classification. Postoperative hospital stay was defined as primary hospital stay after the surgery. Overall hospital stay also included the days after readmission. Mortality was recorded as death within 90 days of surgery.

Statistical analysis

The study was designed simultaneously with another RCT on HC treatment in high-risk PD patients [13]. At that time, it was estimated that HC treatment on high-risk PD-patients lowered the overall complication and fistula rate after PD to one seventh, which was used for the power calculation. Calculations were made prior to the randomized trial. We estimated that 36 consecutive patients scheduled for open distal resection would need to be randomized to show a statistically significant difference (alpha 0.05, 80% power). Due to the estimation of a 10% dropout, 40 patients were randomized.

The statistical analysis was performed using SPSS statistical software. Fisher's exact test for cross-tabulated variables and Mann-Whitney test for quantitative variables were used to calculate the significance between the two groups.

Results

Over the study period of 27 months, 47 patients were scheduled to undergo an open DP for benign or malignant disease. Of these, seven were excluded before randomization: 4 for logistic reasons, 2 did not meet the inclusion criteria and one had a previous PD. The remaining 40 patients were randomized preoperatively. Of these, one was observed to be on ongoing cortisone treatment only after inclusion for randomization, and was excluded from the study prior to surgery. During surgery, five patients were diagnosed with advanced, inoperable disease and three patients went through a different procedure (PD, total pancreatectomy and pseudocystojejunostomy) and were excluded from the study. The remaining 31 patients continued through the study after randomization. Of these, 14 were randomized to the placebo group and 17 to the hydrocortisone group. The flowchart is shown in Fig. 1.

No significant differences in the pre- or perioperative characteristics were found between the hydrocortisone and placebo groups, except that the median age was slightly higher in the HC group, $p = 0.045$. Patient characteristics are shown in Table 1 and the final histopathological diagnoses are seen in Table 2. No difference in previous diseases or drug usage was observed and no octreotide or pasireotide was used for the patients. The percentage of acinar cells at the transsection line analysed intraoperatively from the frozen section was over 40% in all patients. Pancreas texture was also defined as soft for all patients during the operation. Pancreatic duct diameters were similar between the groups, 94% in the HC group and 93% in the placebo group being <3 mm. Operative time was similar in the groups, as was blood loss. The

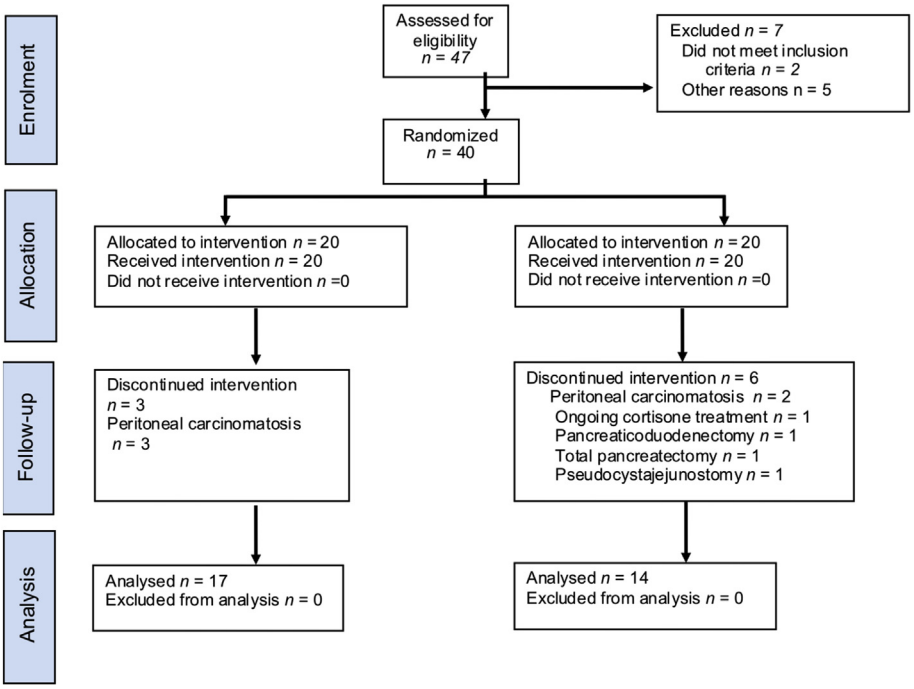

Fig. 1. CONSORT flow diagram for the trial.

Table 1
Pre- and perioperative characteristics of the HC group and the placebo group.

	Hydrocortisone (n = 17)	Placebo (n = 14)	p value
Age yrs, median (range)	73 (41–82)	61 (39–76)	0.045
Male	7 (41%)	4 (29%)	0.707
BMI, kg/m2	27 (22–35)	29 (21–39)	0.164
COPD	1 (6%)	2 (14%)	0.576
Diabetes	7 (41%)	5 (36%)	1.00
ASA class			
I-II	6 (35%)	7 (50%)	0.481
III	11 (65%)	7 (50%)	
Operative time min, median (range)	158 (103–391)	159 (108–224)	0.942
Operative blood loss mL, median (range)	550 (120–2300)	700 (50–1400)	0.975
Main pancreatic duct diameter			
< 3 mm	16 (94%)	13 (93%)	1.00
≥ 3 mm	1 (6%)	1 (7%)	
Splenectomy	12 (71%)	6 (43%)	0.157
Acini >40% in the transsection line	17 (100%)	14 (100%)	1.00
Soft pancreas texture	17 (100%)	14 (100%)	1.00

Table 2
Final histopathological diagnoses in the groups.

	HC	Placebo	P value
Histopathological diagnosis			0.578
Pancreatic ductal adenocarcinoma	4 (23%)	1 (7%)	
NET	2 (12%)	2 (13%)	
Cystic tumour	9 (53%)	8 (57%)	
Other	2 (12%)	3 (21%)	

surgical technique was similar for all patients, the pancreas was cut with a scalpel and the duct was closed and the cut edge was hand sewn. Splenectomy was performed on 70% (12/17) in the HC group and on 42% (6/14) in the placebo group, p = 0.157. These parameters are shown in Table 1.

Primary endpoint

The overall morbidity was 48.4% (15/31), defined as complications graded Grade II or higher on the Clavien-Dindo classification [16]. In the HC group the overall morbidity was 41% (7/17 patients) and in the placebo group 57% (8/14). Major complications (Clavien III-V) occurred in 12.9% (4/31) of all patients. There were no statistically significant differences between the groups, 5.9% (1/17) and 21.4% (3/14) in the HC and placebo group respectively (p = 0.304) The details of complications and their management are presented in Table 3.

Secondary endpoint

The secondary endpoint of this study, the incidence of clinically significant POPF (grades B and C), was 22.6% (7/31) among all patients. In the HC group there was only one Grade C fistula among 17 patients (5.9%). This patient developed sepsis, and needed both percutaneous drainage and endoscopic retrogradic pancreaticography (ERP) to treat the POPF. She also developed a pulmonary embolism.

Table 3
Postoperative complications in the groups. The overall fistula rate was significantly lower in the hydrocortisone group (6% vs 43%). Hydrocortisone also seems to have a favourable effect on major complications (Clavien-Dindo III-V).

	Hydrocortisone (n = 17)	Placebo (n = 14)	P value
Pancreatic fistula			
Overall (B + C)	1 (6%)	6 (43%)	0.028
Grade B	0	4 (29%)	
Grade C	1 (6%)	2 (14%)	
Delayed gastric emptying	1 (6%)	1 (7%)	1.00
Intra-abdominal fluid collection	2 (12%)	3 (21%)	0.636
Wound infection	1 (6%)	3 (21%)	0.304
Intra-abdominal haemorrhage	0	0	
Pneumonia	1 (6%)	2 (14%)	0.576
Spleen necrosis	1 (6%)	1 (7%)	1.00
Lymphatic leak	2 (12%)	1 (7%)	1.00
CT verified pancreatitis	1 (6%)	1 (7%)	1.00
Urine trypsinogen positive ≥ 2 days	4 (24%)	5 (36%)	0.693
Pulmonary embolism	1 (6%)	0	1.00
Clavien-Dindo			
I	4 (24%)	4 (29%)	
II	6 (35%)	5 (36%)	
III	1 (6%)	2 (14%)	
IV	0	0	
V	0	1 (7.1%)	
Clinically significant (III–V)	1 (6%)	3 (21%)	0.304
Reoperation	0	1 (7.1%)	0.452
Total hospital stay (days, range)	8 (2–23)	7 (6–38)	0.625
Readmission	3 (18%)	3 (21%)	1.00
90-day mortality	0	0	

In total, 6/14 (42.9%) clinically significant fistulas developed in the placebo group. Four of these were Grade B fistulas. They were treated with original, intra-operatively placed drain and medical interventions. One Grade C fistula required percutaneous drainage followed by ERP and a pancreatic stent. Another Grade C fistula resulted in the patient's death on day 96 post-operatively. He was readmitted for infected collection of fluid and treated with a percutaneous radiologic drain and an endoscopic stent for collection. Finally the patient developed an intestinal necrosis seen in laparotomy due atherosclerosis and attributed to prolonged infection. With HC treatment the rate of clinically relevant POPF (5.9% vs 42.9%, p = 0.0281) was significantly lower compared to that in the placebo group. Fig. 2.

The incidence of former grade A POPF, also called a biochemical leak, was 22.6% (7/31) among all patients: 6 in the HC group and 1 in the placebo group (ns). These fistulas had no impact on the treatment of the patient. Thus, the overall incidence of any POPF was 45.2%: 22.5% grade A, 12.9% grade B and 9.6% grade C. The overall incidence of any POPF was similar in the two groups, but, interestingly, six out of the seven clinically relevant grade B–C fistulas were seen in the placebo group, whereas in the HC group almost only grade A fistulas were seen.

HC treatment was well tolerated and no adverse events occurred. The rates of wound infections and other infections were similar in the HC and placebo groups. Length of primary or total hospital stay did not differ between the groups with 8 (3–23) vs. 7 (6–38) days' total stay and 7 (6–14) and 8 (3–16) days' primary stay.

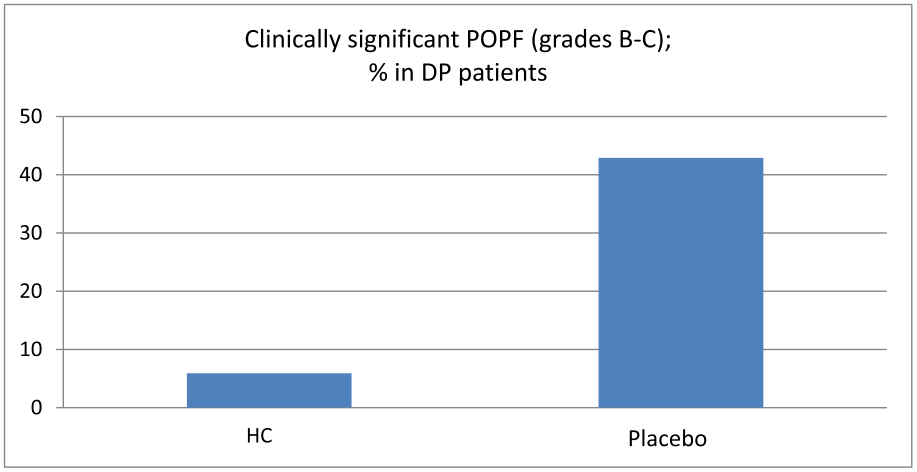

Fig. 2. Hydrocortisone treatment significantly reduced the rate of clinically significant POPF (5.9% vs 42.9%, p = 0.0281.

The readmission rates were similar: 17.6% and 21.4% respectively in the HC and placebo groups. Of these, in the HC group one patient had a spleen necrosis diagnosed on the twelfth postoperative day and one patient had an intra-abdominal haematoma diagnosed on the 24th postoperative day. Both were completely healed with no need for invasive procedures.

In both groups 90-day mortality was zero.

Discussion

Postoperative pancreatic fistula remains the most common complication after DP. In our recent randomized trial we showed that perioperative HC treatment reduces Clavien-Dindo 3–5 complications after PD, and also the clinically relevant POPF rate tended to be lower (11% vs. 27%). The present study was run partly concomitant with the PD RCT with the same protocol. Our main finding was that HC treatment significantly reduced the risk of POPF after DP from 43% to 5.9%. A tendency for fewer overall Clavien-Dindo III-V complications in the HC group was also seen.

Many recent RCTs have tried to lower the fistula rate after DP. The multicentre randomized DISPACT trial in 2011 found no difference between the stapler and hand-sewn group in the incidence of pancreatic fistula: 32% vs. 28% [5]. However, some meta-analyses have reported reduction in fistula rates after stapler closure [1,17]. Resection with a stapler reinforced with absorbable materials has been shown to reduce POPF, the B and C fistula rate being 1.9% among patients with mesh reinforcement vs. 20% of the patients without mesh in the stapler line [6]. The Tachocil patch has been shown in two RCTs not to lower the incidence of POPF [18]. However, adding a seromuscular patch to the staple line significantly decreased morbidity, but the clinically different POPF rate was similar [19]. Teres ligament patch reduced the complications after DP, but the clinically relevant fistula rate was not reduced [20]. Pancreaticojejunal anastomosis and pancreaticogastrostomy of the pancreatic stump have also been used without a significant decrease in fistula rate [9,21,22]. Preoperative endoscopic pancreatic stenting was studied in one prospective single-institution RCT in Sweden and did not reduce PF after DP [10]. Inducing relaxation of the Sphincter of Oddi by endoscopic botulinum toxin injection is promising according to one non-randomized trial having a B/C fistula rate of 0% vs. 33% and an RCT to clarify the effect is ongoing in Germany [11].

On the pharmaceutical side, octreotide and pasireotide have been investigated. Octreotide has showed a reduction in overall fistula rate after pancreas surgery, but no difference was found in clinically relevant POPF [23]. Somatostatin analogue pasireotide significantly reduced the incidence of clinically relevant pancreatic fistula in a recent RCT to as low as 7% [12].

In this study HC treatment reduced the clinically relevant B/C fistula rate to 5.9%, which is equivalent to the low fistula rates reported in the studies before [5,6]. For instance, pasireotide treatment reduced the B/C fistula rate from 23% to 7% in patients undergoing DP [12]. Difference was found only on clinically relevant POPF, not among Grade C fistulas only. The overall incidence of clinically relevant POPF in the placebo group of this study was 42%, within the range reported in earlier studies with open DP [10,12,20,24]. In our series less than 10% of the patients had corpus tail resections, without difference between the groups. This partly explains the fistula rate, as tail resections have been reported to carry a higher incidence of POPF compared to corpus + tail resections [25].

Severe complications (Clavien-Dindo III-V) tended to occur less often in the HC group than in the placebo group (5.9% and 21.4; ns; $p = 0.30$ respectively). Furthermore, the rate of severe complications in the HC group (5.9%) was less than half of the rate of severe complications reported in a recent RCT comparing PJ and stapler closure 11.3% vs. 13.1% [21].

The prevalence of splenectomy was 71% in the HC group and 43% in the placebo group (ns). No association to the POPF or overall complications was seen in the splenectomized patients or in the patients where the spleen was saved. There was one spleen necrosis detected in both groups, both of these healed conservatively and were graded as Clavien-Dindo grade II complications. The rates of wound infections and other infections as well as the readmission rates were similar in the HC and placebo groups. There was one death on the 96th day in the placebo group, which was not included in 90-day mortality since it did not occur during the initial admission: The patient was readmitted and died of bowel necrosis caused by prolonged infection and atherosclerosis.

This study was performed partly simultaneously with the RCT on PD with the same HC/placebo protocol [13], but designed to be presented separately, mainly because of the different POPF and complication profiles of PD and DP. By separating these studies, we give valuable information to the field on these two different operations. If the results are combined, the overall incidence of clinically significant POPF is 8.9% in the HC group and 27.1% in the placebo group ($p = 0.032$). Thus HC seems to be effective in reducing clinically significant fistula overall in open pancreatic resections. As comparing these two studies, the effect of HC treatment on fistula rate seems to be higher after DP than after PD. The mechanism of fistula formation after DP is somewhat different compared to that after PD. Presumably after both operations, HC decreases inflammation and oedema in the pancreatic tissue. One may speculate that in the DP operation this effect is enough to create a lower pressure inside the pancreatic duct, enabling a better flow towards duodenum, thus preventing the formation of a fistula. In PD operation the prevention of fistula may be more complex, as also a good healing of the pancreatico-jejunal anastomosis is needed to prevent a fistula.

High frequency of acinar cells (>40%) in the cut edge of the pancreas increases the risk of postoperative complications and is an objective method to recognize the soft, nonfibrotic pancreas [14]. In our hospital acinar cells in PD and DP are nowadays counted routinely by a pathologist perioperatively from a frozen section to identify patients at risk of complications. In general, the majority of DP patients are at high risk of complications and have an acinar-rich cut edge and thus a high incidence of POPF. Unlike with the pancreatic head tumors, distally located tumors do not occlude pancreatic flow in the remaining pancreas, and thus in the remaining pancreas less fibrosis and more acinar cells as well as a normal pancreatic duct are present. Also on the present study all patients had an acinar-rich high-risk soft pancreas with a non-dilated duct, and thus the tumour pathology did not seem have an effect on the individuals' risk to develop a POPF.

The HC dose we used was identical to that used in the other RCT in PD patients. Also in this study the peri-operative use of 100 mg of hydrocortisone three times a day was confirmed safe [13]. Similarly, a study using it to prevent atrial fibrillation in cardiac surgery found it safe without any increase in adverse effects such as wound infection or stomach ulcers [26]. HC treatment in our study was also well tolerated, and no adverse events occurred. With pasireotide the most common adverse events were dose-limiting nausea (17%) and hyperglycaemia [12].

We hypothesize that POPF and other complications occur after postoperative pancreatic inflammation. Earlier we have reported that a large proportion of acinar cells at the transection line of the pancreas indicate a significant risk for complications. We have also demonstrated that the inflammation cascade at the transection line of the pancreas begins early and that the peak activation of inflammation markers (NF-kB and MCP-1) can be seen within 4 h of

surgical trauma. Recently it was shown that postoperative acute pancreatitis is associated with increased occurrence of POPF and overall morbidity after PD [27] In this study the activation was significantly higher in acinar cell rich pancreata than in fibrotic pancreata [14]. These findings led us to hypothesize that postoperative inflammation increases complications, and that we might be able to reduce the complications with corticosteroid treatment. In our pancreas laboratory we are currently performing mechanistic studies on the effect of hydrocortisone on experimental acute pancreatitis, but at the moment it is too early to speculate with the mechanisms. We assume that the favourable effect of HC is not only "local", but also systematic. Cortisone has been used in experimental acute pancreatitis in animal models [28,29] and also in the treatment of autoimmune pancreatitis [30]. Interestingly, corticosteroids have not been shown to reduce post-ERCP pancreatitis [31] nor to reduce trypsinogen leak after PD [13]. However, the aetiology of the inflammation process due to surgical trauma may differ from that arising in ERCP, which should be a subject for further research.

The strength of this study was that all patients were high-risk patients, having a soft pancreas and narrow pancreatic duct. This was confirmed by analysing the acini in the transection line, considered more objective and not based on the surgeons' subjective estimates of gland texture. All patients had a standardized, similar open tail resection (to standardize the pancreatic trauma). The small number of patients in each group was the main weakness of this study. Likewise the fact that we included only open procedures. At the moment we are using the HC treatment as a routine even for laparoscopic distal resections. Thus we would recommend the use for laparoscopic operations also, even though this has not been shown in a study. However, larger studies are needed to confirm our findings.

HC treatment seems to be a safe, inexpensive and well-tolerated pharmaceutical method in preventing POPF after DP. Among drugs so far only pasireotide has been shown to have a significant effect on POPF after DP, a similar effect on lowering the fistula and complication rate than HC, but seems to have some adverse events. The cost-effectiveness of pasireotide has also been studied and did not increase the overall cost of pancreatic resection [32], but might save costs within the health care system [33]. Nevertheless, the costs using pasireotide are considerably higher than the cost of inexpensive HC treatment, which necessitates further comparative studies with cost-analysis.

For future studies it would also be important to validate the system to confirm a "soft" high-risk pancreas. Acinar cell count is an easy and objective intraoperative method to identify patients at high risk for POPF [14]. This method is routinely used in our hospital among PD and DP patients as is perioperative HC treatment for patients deemed to have a high risk for complications. On the other hand, HC treatment is discontinued after the initial dose if the intra-operative acinar cell analysis renders the patient low-risk for POPF.

In conclusion, perioperative HC treatment reduces the incidence of clinically significant fistula after open distal pancreatectomy. The frequency of POPF after HC treatment is low also when compared to other means of POPF prevention studied earlier. Overall in open pancreatic surgery (PD and DP), HC seems to be effective in reducing clinically significant fistula and may have a favourable effect also on overall complications.

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