Low-dose heparin for the prevention of post-ERCP pancreatitis: a randomized placebo-controlled trial

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Abstract

Background As suggested by observational and animal studies, heparin has antiinflammatory effects that could prevent acute post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Low-molecular-weight heparin did not reduce the incidence of post-ERCP pancreatitis in a controlled study. The current study aimed to determine whether prophylactic administration of low-dose unfractionated heparin, which has potentially more antiinflammatory capability, can prevent acute post-ERCP pancreatitis.

Methods Patients scheduled for ERCP in the authors’ department were randomized to receive unfractionated heparin (5,000 IU) or placebo (saline solution 0.5 ml) administered subcutaneously 20 to 30 min before the ERCP. Patients who had undergone endoscopic sphincterotomy in the past were excluded from the study. Post-ERCP pancreatitis was defined according to criteria established by Cotton: abdominal pain combined with a threefold elevation of blood amylase 24 h after the ERCP.

Results The study enrolled 106 patients. One patient was excluded from the analysis due to inaccessible papilla of Vater, leaving 51 patients in the heparin group and 54 in the placebo group, for a total of 105 patients (62 women and 43 men) with a mean age of 64.6 years. The rate of post-ERCP pancreatitis was not different between the groups (heparin, 4 patients, 7.8%; placebo, 4 patients, 7.4%). Two patients in each group experienced mild bleeding.

Conclusions The study did not demonstrate a significant effect of low-dose unfractionated heparin in the prevention of post-ERCP pancreatitis. A multicenter trial with a larger number of patients is needed to demonstrate a benefit from this drug.

Keywords Clinical papers/trials/research · Complications · Endoscopic retrograde cholangiopancreatography · ERCP · Pancreatic

Acute pancreatitis, the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), is experienced by 1% to 10% of patients [1–3]. Although rarely fatal, post-ERCP pancreatitis is associated with significant discomfort for patients and increased use of health care resources. Prophylactic means are therefore urgently needed to prevent pancreatitis after ERCP.

Several pharmacologic agents have been studied in relation to their potential for preventing post–ERCP pancreatitis, but results have been mixed or negative [4–11]. Gabexate mesylate was shown to be efficacious in a large prospective trial, but this drug is expensive and difficult to use [12]. The same is true for interleukin-10 (IL-10) [13]. The prophylactic use of octreotide diminished the rate of post ERCP hyperamylasemia for patients with chronic obstructive pancreatitis and those with an endoscopic sphincterotomy, but did not alter the frequency of post-ERCP pancreatitis [14].

A paper recently published by Thomopoulos et al. [15] shows that subcutaneous administration of octreotide at high doses 24 h before and after ERCP protects against...
acute post-ERCP pancreatitis. There are, however, some drawbacks with this strategy. Outpatients should be taught to give themselves subcutaneous octreotide, which often is not feasible. Gastric stasis was noted in 35% of patients despite a prolonged fast, and the cost of treatment was relatively high.

Prophylactic temporary stenting of the pancreatic duct has been shown to reduce the risk of post-ERCP pancreatitis in randomized controlled studies [16–19]. However, a second endoscopy may be required for stent retrieval, raising the overall cost of treatment.

Heparin inhibits pancreatic proteases in both plasma and pancreatic tissue in animal models of acute pancreatitis, improves pancreatic microcirculation, and inhibits inflammatory cascade [20–28]. Salas et al. [25] reported that heparin inhibits tumor necrosis factor (TNF)-induced interactions of leukocytes and endothelium, thereby reducing inflammation. When inflammation was stimulated in vitro with IL-1, bacterial lipopolysaccharide, or tumor necrosis factor, Leever et al. [26] found that leukocyte–endothelium interactions were inhibited by three types of heparin and even by a heparin derivative without anticoagulant activity. Thus the antiinflammatory effect of the different heparin types does not depend on the anticoagulant properties, but rather on the capability to prevent the special ligands associated with the interaction of leukocytes and endothelium.

Koenig et al. [27] reported that unfractionated heparin is an excellent inhibitor of L-selectin (expressed on leukocytes) and P-selectin (expressed on platelets and activated endothelial cells). Even at concentrations much lower than those recommended for therapeutic anticoagulation, the heparin-induced inhibition of L- and P-selectin interactions with their natural ligands P-selectin glycoprotein ligand-1 (i.e., PSGL-1) is essentially complete.

Rabenstein et al. [29] prospectively evaluated potential risk factors for acute pancreatitis in 812 ERCP procedures with endoscopic sphincterotomy. In this series, heparin was administered for various clinical reasons (unrelated to ERCP) to 32.9% of the patients (n = 268), with 208 receiving low-molecular-weight heparin (LMWH) and 60 receiving unfractionated heparin. A group of 547 patients who did not receive heparin served as a control.

The frequency of acute pancreatitis was significantly lower in the heparin group (3.4%) than in the control group (7.9%; p = 0.005). The patients who received LMWH had a 4.3% rate of post-ERCP pancreatitis, whereas the rate for patients receiving unfractionated heparin (both low dose and high dose) was 0.

However, in a controlled study, LMWH did not reduce the incidence of post-ERCP pancreatitis [30]. The aim of our randomized, double-blind, placebo-controlled study was to evaluate the effectiveness of low-dose unfractionated heparin for preventing post-ERCP pancreatitis.

Patients and methods

Patients 18 years of age or older referred to our center for ERCP on an in- or outpatient basis were eligible for enrollment in the study. Exclusion criteria specified previous ERCP with sphincterotomy, acute or chronic pancreatitis, treatment with LMWH, unfractionated heparin, oral warfarin or aspirin within 5 days before the procedure, mental impairment, known hypersensitivity to heparin, history of a coagulation disorder, active bleeding, platelet count less than 50,000/µl, and pregnancy. Informed consent was obtained from all patients participating in the trial. The study was approved by the Ethics Committee of Tel Aviv Sourasky Medical Center.

Baseline data collection

The serum amylase level was determined immediately before ERCP. The following information was collected from every patient: demographic data (age, gender), indication for ERCP, previous episodes of pancreatitis, previous cholecystectomy, and bilirubin level.

Randomization

Patients with no exclusion factors were consecutively randomized to the heparin or the control group. The patients in the former group received a deep subcutaneous injection of heparin 5,000 IU in the abdominal fat layer 20 to 30 min before ERCP. The patients in the control group received 0.9% saline (indistinguishable from the heparin injection) applied in the same way. Randomization and injection were carried out by personnel not involved in the endoscopic procedure or the clinical care of the patients. The patient, the endoscopist, the post-ERCP care team, and the individual evaluating the outcome were unaware of the treatment or placebo administration.

Endoscopic procedure

All endoscopic procedures were performed by a physician experienced in therapeutic ERCP. The procedure was performed with the patient under intravenous sedation by phentanyl (0.05–0.15 mg) and midazolam (5–15 mg). The patients were monitored by pulse oximetry and electrocardiogram, and supplemental oxygen was administered. The procedures were performed with a Pentax duodenoscope (ED 3680 TK; Pentax, Tokyo, Japan) and standard cannulation devices (various manufacturers at random). Contrast medium (60% sodium and meglumine amide...
triazoate diluted in distilled water) was injected manually under fluoroscopic guidance. Selective cannulation of the bile, pancreatic duct, or both was attempted in all cases. To inhibit excessive duodenal peristalsis, up to three boluses of hyoscine-n-butyl bromide 10 mg were administered intravenously. Endoscopic sphincterotomy was performed using the endocut electrosurgical current (ERBE ICC 200, ERBE Elektromedizin; GmbH, Tübingen, Germany).

The following information was recorded during the procedure: final ERCP diagnosis, common bile duct diameter, type of procedure performed (pancreatography, sphincterotomy, precut papillotomy), repeated pancreatic injections, and “difficult cannulation.” A cannulation was considered to be “difficult” when selective biliary cannulation was intended but unsuccessful, preceded by repeated cannulation or injection of the main pancreatic duct (i.e., >3 times), accomplished only after a precut papillotomy, or achieved after more than 20 min.

Follow-up assessment

Outpatients who underwent ERCP were discharged 2 to 3 h after the procedure unless they experienced persistent abdominal pain or other clinical manifestations of ERCP-related complications. They were instructed to return 24 h later to be evaluated for clinical evidence of any complication and to obtain blood specimens for determination of amylase level.

Hospitalized patients were returned to their department immediately after ERCP and monitored for the development of complications by the department staff. On the following day, they were evaluated for clinical evidence of any complication, and a blood sample for determination of amylase level was obtained. All patients were contacted by phone (if ambulatory or discharged) or by a visit in the department 72 h after the procedure for assessment of any late ERCP complication or adverse effect of the study drug. All side effects were reported to the Ethics Committee of Tel Aviv Sourasky Medical Center.

Study end points

The main end point of this study was the frequency of post-ERCP pancreatitis in each group. This was defined as pain persisting for 24 h and associated with a threefold increase in serum amylase. Pancreatitis was classified as mild, moderate, or severe according to days of hospital stay, as proposed by Cotton et al. [31], when no other cause for hospital stay was present. Otherwise, clinical (Ranson’s [32] score) and computed tomography (CT) results (Balthazar’s [33] score) were used as indicators of severity. The secondary end point was the number of patients with severe pancreatitis (defined as a hospital stay exceeding 10 days, fluid collection or intervention [31], Ranson’s [32] score exceeding 3, or Balthazar’s [33] score of D or E) in each group.

Number of patients

We assumed that the rate of post-ERCP pancreatitis would be about 10% and that prophylactic treatment with heparin would reduce this rate to 3%. Therefore, the number of patients required for a statistical power of 80% would be 190 per group.

Results

A total of 106 patients were recruited. For one patient in the heparin group, who had undergone a Billroth II operation, the papilla was inaccessible due to the length of the afferent loop. Therefore, he was excluded from the analysis, leaving 51 patients in the heparin group and 54 patients in the placebo group, for a total of 105 patients (62 women and 43 men) with a mean age of 64.6 years. A total of 56 patients (53.3%) underwent ERCP on an outpatient basis. The ERCP demonstrated choledocholithiasis for 54 patients (51.4%), pancreatic or biliary cancer for 22 patients (21%), and other biliary diseases for 9 patients (8.6%). The ERCP results were normal for 15 patients (14.3%). Failed cannulation occurred for five patients (4.8%). Precut papillotomy was required for cannulation of the common bile duct in 13 patients (12.4%), and biliary sphincterotomy was performed for 100 patients (95.2%).

A total of 20 procedures (19%) were considered “difficult,” as defined earlier. The groups were similar in terms of baseline clinical data, final ERCP diagnosis, and endoscopic therapeutic maneuvers (Tables 1 and 2).

Overall, post-ERCP pancreatitis developed in 8 of the 105 patients (7.6%). The rate of post-ERCP pancreatitis was not different between the groups (heparin, 4 patients, 7.84%; placebo, 4 patients, 7.4%). One episode of pancreatitis in the heparin group and two episodes in the placebo group were graded severe. There were no fatal cases of pancreatitis.

Asymptomatic elevation of the serum amylase level more than three times the baseline was observed in nine patients in the heparin group (17.6%) and 7 patients in the placebo group (13%) (nonsignificant difference).

Mild bleeding after sphincterotomy occurred for two patients in the heparin group and two patients in the placebo group. All bleeding episodes resolved during the ERCP procedure either spontaneously or after adrenaline...
In a prospective analysis of risk factors for acute post-ERCP pancreatitis, Rabenstein et al. [29] found that any type of heparin administered to patients undergoing ERCP with endoscopic sphincterotomy was associated with a significantly lower frequency of pancreatitis (3.4%) than found in patients who did not receive heparin (7.9%). Because the study was nonrandomized, confounding effects of other variables or conditions associated with the indication for heparin administration that might have influenced the low frequency of pancreatitis in the heparin group could not be excluded. Therefore, the same researchers later conducted a prospective randomized controlled study to verify their observations [30]. In the later study, a LMWH (Certoparin) was used but offered no benefit compared with placebo based on the frequency and severity of acute post-ERCP pancreatitis. The authors speculated that the discrepancy between the results of this clinical trial and the experimentally proven effects of heparin [20–28] might be explained by the drug chosen for the study. It is possible that the antiinflammatory capability of the heparin molecule is destroyed during the fragmentation process. Indeed, Koenig et al. [27] have shown that LMWH is much less capable of inhibiting L- and P-selectin than unfractionated heparin.

This study aimed to determine whether unfractionated heparin (instead of LMWH) can decrease the frequency and/or severity of post-ERCP pancreatitis. The only clinical evidence for this possibility comes from the initial, nonrandomized study of Rabenstein et al. [29]. In that study, no pancreatitis was experienced by 60 patients who received unfractionated heparin (12,000–15,000 IU/day subcutaneously or intravenously for 41 patients; 25,000–30,000 IU/day intravenously for 19 patients from at least 24 h before ERCP until 24 h after ERCP). In the current randomized controlled study, we found no difference in the number of pancreatitis cases between the heparin and placebo groups. Actually, the incidence of pancreatitis was slightly higher in the heparin group.

This discrepancy between the results of our study and the study of Rabenstein et al. [29] could be explained by several factors. First and most important, the lack of randomization in the study of Rabenstein et al. [29] could have led to confounding effects of other variables or conditions associated with the indication for heparin administration that might have a potential to decrease the incidence of post-ERCP pancreatitis. Second, about one-third of the patients in the study of Rabenstein et al. [29] (19 of 60) received a high dose of heparin (25,000–30,000 IU/day administered intravenously). The remaining two-thirds of the patients received a much lower dose of heparin (12,000–15,000 IU/day), but this dose still was higher than the one used in our study. Finally, in the study of Rabenstein et al. [29], the patients received multiple doses of heparin from at least 24 h before ERCP until 24 h afterward. We chose to give our patients only one prophylactic low dose of heparin (5,000 IU administered subcutaneously) 20 to 30 min before the ERCP based on the pharmacokinetics of the drug [34].

Our study did not demonstrate a significant effect of low-dose unfractionated heparin in the prevention of post-ERCP pancreatitis. Obviously, the current study lacked sufficient

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**Table 1** Baseline clinical data

<table>
<thead>
<tr>
<th></th>
<th>Heparin group (n = 51)</th>
<th>Placebo group (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean</td>
<td>65.2 ± 14.5</td>
<td>63.9 ± 14.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>20/31</td>
<td>23/31</td>
</tr>
<tr>
<td>Hospitalized/ambulatory</td>
<td>22/29</td>
<td>27/27</td>
</tr>
<tr>
<td>Previous Bilroth II operation: n (%)</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Previous cholecystectomy: n (%)</td>
<td>17 (33.3)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Bilirubin median (range), mg/dl</td>
<td>2.78 (0.46–26)</td>
<td>2.55 (0.4–28)</td>
</tr>
<tr>
<td>Amylase level &gt;180 U/l: n (%)</td>
<td>2 (3.9)</td>
<td>3 (5.6)</td>
</tr>
</tbody>
</table>

**Table 2** Endoscopy-related information

<table>
<thead>
<tr>
<th></th>
<th>Heparin group (n = 51)</th>
<th>Placebo group (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General anesthesia</td>
<td>6 (11.8)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Intended duct for cannulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>51 (100)</td>
<td>54 (100)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Final ERCP diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>25 (49)</td>
<td>29 (53.7)</td>
</tr>
<tr>
<td>Biliary/pancreatic cancer</td>
<td>13 (25.5)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Normal cholangiogram</td>
<td>7 (13.7)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (7.8)</td>
<td>5 (9.3)</td>
</tr>
<tr>
<td>Failed cannulation</td>
<td>2 (3.9)</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>Difficult cannulation</td>
<td>10 (19.6)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Biliary sphincterotomy</td>
<td>49 (96)</td>
<td>51 (94.4)</td>
</tr>
<tr>
<td>Precut papillotomy</td>
<td>6 (11.8)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Pancreatic injection</td>
<td>8 (15.7)</td>
<td>6 (20.4)</td>
</tr>
<tr>
<td>CBD diameter ≥10 mm</td>
<td>26 (50.1)</td>
<td>26 (48.1)</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

diluted in saline (1:20000) was sprayed over the papilla area. There were no other complications in either group.

**Discussion**

Compared with other therapeutic agents that might possibly be used to reduce the frequency of post-ERCP pancreatitis, low-dose heparin has a number of advantages: ease of use, low cost, administration on an out-patient basis, and low incidence of side effects.

In a prospective analysis of risk factors for acute post-ERCP pancreatitis, Rabenstein et al. [29] found that any type of heparin administered to patients undergoing ERCP with endoscopic sphincterotomy was associated with a significantly lower frequency of pancreatitis (3.4%) than found in patients who did not receive heparin (7.9%). Because the
statistical power to reveal a more modest effect of low-dose heparin. With 51 and 54 patients per group, the power of a one-sided test to detect a difference significant at the 5% level when the probabilities were 0.03 and 0.10, respectively, was only about 45%. The number of patients was lower than planned because the study was conducted in a single center, and patients with previous sphincterotomy were excluded (due to a very low risk of post-ERCP pancreatitis).

Despite the disappointing results of the current study, unfractionated heparin could be included in future trials because there is a rationale for its use. The need for larger groups of patients means that a multicenter study would be necessary to demonstrate a possible benefit of heparin. It should be kept in mind, however, that the prophylactic use of low-dose heparin lacked even a slight tendency to prevent post-ERCP pancreatitis in the current study. Therefore, the effect of heparin that might be demonstrated as statistically significant in a larger multicenter study may result in a high number of patients needing to be treated.

One possibility is to increase the dose and/or duration of heparin treatment in future trials. However, this might expose patients to a higher risk of post-sphincterotomy bleeding. In the study of Rabenstein et al. [29] the incidence of post-sphincterotomy bleeding among patients receiving low-dose unfractionated heparin was 2.4% compared with 5.3% among patients receiving high-dose unfractionated heparin. This difference did not reach statistical significance due to the small number of patients in the two groups, but may become clinically relevant in a larger cohort of patients. Longer duration of heparin treatment, on the other hand, may be inconvenient and thus less attractive.

There is no doubt that the single most important way to reduce the post-ERCP pancreatitis rate is to avoid performing ERCP for marginal indications, especially for patients at higher risk of complications. Clinicians should avoid using ERCP when the probability of finding stones or other obstructive pathology is low to intermediate [35]. In our institution, we widely use alternative imaging techniques such as magnetic resonance cholangiopancreatography and endoscopic ultrasonography to exclude obstructive biliary pathology. Therefore, the rate of normal ERCP findings in our study was low (14.3% of all cases).

In summary, our study did not demonstrate a significant effect of low-dose unfractionated heparin in the prevention of post-ERCP pancreatitis. A multicenter trial with a larger number of patients would be needed to demonstrate a possible benefit from this drug.

References


