Original Article
The effect of post-contrast washıng on post-endoscopıc retrograde cholangıopancreatography pancreatıtıs

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Abstract: Objective: We aimed to evaluate the efficacy of dilutional washing with saline solution following the administration of contrast agent for ERCP in decreasing the rate of pancreatitis, in our experimental rat model. Methods: Fourty Wistar-Albino® male rats of 250-300 g were divided into 4 equal groups. Group 1: Cannulation, Group 2: Cannulation+saline, Group 3: Cannulation+contrast agent, Group 4: Cannulation+contrast agent+saline. At the 24th hour following the procedures, the rats were sacrified and pancreatic tissues were examined histopathologically, with the evaluation of blood levels of leukocyte, glucose, (SGOT), (LDH), amylase, C-reactive protein (CRP) and acid-base status. Histopathological grading of acute pancreatitis was performed using haematoxylin and eosin staining. Results: Mean levels of amylase, leukocyte, AST and LDH were found to be significantly higher in groups 2, 3, 4 when compared to group 1 (P<0.05). CRP level was found to be highest in group 3 (P>0.05). Histopathological grade of pancreatitis was found to be significantly higher in groups 2, 3, 4 when compared to group 1 (P<0.05). Scores of edema, acinar necrosis and amylase level were found to be higher in group 3 than group 4. Scores were similar in groups 2 and 4. Conclusion: We found that dilution with saline solution during ERCP procedure may be beneficial in decreasing the rate of post ERCP pancreatitis, which is shown with histopathological and laboratory findings. We suggest dilutional washing out of the contrast agent at low pressures following the ERCP procedure.

Keywords: Post ERCP pancreatitis, experimental pancreatitis, contrast induced pancreatitis

Introduction

The incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is reported to be between 2-10% (2-4% in low risk group and 0-5% in high risk group) [1]. Post-ERCP pancreatitis is a serious complication of the procedure and etiology is multifactorial [2]. The clinical progress is mild in 85-90% of the patients, and necrotising pancreatitis with multi-organ failure is encountered in 10-15% of the patients.

Although the underlying mechanisms are not clear yet, it is thought to be single or combined effects of mechanical, chemical, hydrostatic, enzymatic, microbiological, allergic and thermal mechanisms [3-5].

In ERCP procedure, contrast agent is administered directly into common bile duct (CBD) and Wirsung. Due to the suggested theory, contrast agent causes damage on the acinar cells with direct contact [5]. Although various medications and technical variations are suggested in means of minimizing the rate of post ERCP pancreatitis, studies evaluating the effect of the dilution of the contrast agent are very limited [6, 7].

In our study, we aimed to evaluate the efficiency of the dilutional effect of saline solution in decreasing the toxic damage of contrast agent on pancreatic tissue, leading to pancreatitis, in an experimental rat model.

Material and methods

Following the Animal Research Ethics Committee approval, the research was conducted at the Experimental Surgery, Research and Animal Laboratory of Bezmialem University
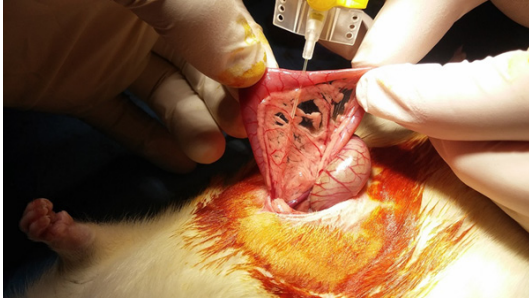
Figure 1. Transduodenal cannulation of common pancreaticobiliary duct.

Faculty of Medicine, Istanbul, Turkey. Fourty Wistar-Albino® male rats of 250-300 g were seperated into 4 randomized groups, with 10 rats in each of them. All the experimental protocols were carried out in accordance with the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences.

All rats were housed under standard laboratory conditions at room temperature with 12 h light/12 h dark cycle and allowed to have ad libitum food and water before and after surgery. During the experimental procedure, the animals were individually placed in cages and kept at room temperature (22°C). All surgical procedures were performed under sterile conditions.

Experimental protocol

Before the experimental procedure, all animals were weighed and the results were recorded. Rats were anaesthetized with intramuscular injections of ketamine hydrochloride (50 mg/kg, Ketalar; Parke-Davis, Morris Plains, NJ) and Xylazine (10 mg/kg, Rompun; Bayer, Istanbul).

In our experimental model, bile duct was cannulated transduodenally, and following the clamping of the hepatic duct with a bulldog clamp, saline solution and contrast agent were administered at 30 mmHg pressure. With this procedure, an ERCP procedure in obstructive cases that lead to retrograde flow of bile to the pancreatic duct, such as stasis due to choledochal stones, edema and tumors of pancreatic head was simulated (**Figure 1**).

A steady pressure of 30 mmHg was chosen as the most appropriate pressure in the light of the recent literature (5.lit.6.kaynak ve tufan tezi). A sphygmomanometer cuff of a pediatric blood pressure device was prepared to deliver 100 cc of isotonic NaCl mediflex or 50% diluted contrast agent under 30 mmHg pressure. The contrast agent used was Ultravist® 300 (Schering, Germany).

Surgical procedure

Fourty Wistar-Albino® rats were assigned in four groups, as follows: The rats were shaved and then prepared with povidone-iodine. A midline (5 cm) laparotomy was performed. Then, the abdominal organs were explored. In all groups, common biliopancreatic duct was cannulated transduodenally via median laparotomy using 24 G catheters. For group 2, 3 and 4, solutions (contrast agent and isotonic NaCl) were infused following theclosure of both ends of the duct at 30 mmHg pressure.

Group 1 (Cannulation group, n=10): Common biliopancreatic ductwascannulated via median laparotomy by a 24 G cannula and the abdomen was closed without performing any other procedure.

Group 2 (Isotonic group, n=10): Common biliopancreatic duct was cannulated transduodenally via median laparotomy by a 24 G cannula. After applying a small bulldog clamp to the hepatic duct, 0.5 ml isotonic NaCl (saline) wasinjected at 30 mmHg pressure.

Group 3 (Contrast group, n=10): Common biliopancreatic duct wascannulated transduodenally via median laparotomy by a 24 G cannula and after applying a small bulldog clamp to the hepatic duct, 0.5 ml 50% diluted contrast agent was injected at 30 mmHg pressure.

Group 4 (Contrast plusisotonic group, n=10): Common biliopancreatic duct was cannulated transduodenally via median laparotomy by a 24 G cannula after applying a small bulldog clamp to the hepatic duct and 0.5 ml 50% diluted contrastagent was injected at 30 mmHg pressure. Later, 0.5 ml isotonic NaCl (saline) was injected at 30 mmHg pressure. The abdomen was closed with 3-0 silk suture in all of the groups.

After 24 hours, all rats were re-anesthetized. Following laparotomy, blood samples were collected via intra-cardiac route for biochemical and blood gas analysis, then the rats were sacrificed by cervical dislocation. The duodenal

Table 1. Mean and madian laboratory blood values of the groups

Laboratory marker	Grup1 Mean ± std median	Grup2 Mean ± std median	Grup3 Mean ± std median	Grup4 Mean ± std median	KW	P value
Weight	428.6±25.29 422.5	418.3±28.46 424.5	402.2±51.99 390.5	408±45.17 424	2.109	0.550
Leukocyte	7.753±2.088 8.095	12.367±2.879 12.275	15.127±5.578 13.645	12.413±4.372 12.255	15.950	0.001
Glucose	125.5±48.34 111.5	160.3±42.22 134	206.6±39.15 206	120.5±23.83 125.5	17.871	0.000
Ph	7.233±0.45 7.232	7.338±0.79 7.316	7.308±0.76 7.341	7.339±0.52 7.344	14.481	0.002
PO_2	56.92±8.72 54.5	46.46±8 48.25	24.81±8.96 24.6	41.15±18.56 34.55	23.066	0.000
HCO_3	21.75±1.28 22	29.07±5 28.7	30.59±7.61 30.15	31.29±3.24 31.25	18.754	0.000
BE	10.07±2.72 9.9	3.27±5.94 2.9	4.3±7.41 3.35	5.51±3.17 5.75	12.053	0.007
Platealet	785200±93786.75 765000	796100±96776.31 789000	665800±267734.03 778000	818400±142320 871000	2.942	0.401
CRP	0.27±0.25 0.21	0.18±0.04 0.19	0.40±0.40 0.17	0.24±0.26 0.16	1.018	0.797
LDH	777.4±387.52 672.5	1165.5±523.76 949.5	1809.7±454.5 1946.5	1547.7±311.57 1562.5	18.881	0.000
Amylase	2602.1±1338.1 2613	4114.6±1190.8 3851	6454.8±1529.7 6609	4700.2±1693.3 4974	19.752	0.000
AST	479.3±135.5 533	748.2±126.8 711	977.5±228.6 965	800.2±310.6 733.5	21.388	0.000

KW: Kruskal-Wallis. AST: Aspartate Aminotransferase. LDH: Lactate dehydrogenase. CRP: C-reactive protein.

Table 2. Intergroup comparison of blood analysis

Groups	Weight	Leukocyte	Glucose	Ph	PO_2	HCO_3	BE	Platelet	CRP	LDH	Amylase	AST
Group 1/Group 2	0.820	0.001	0.034	0.001	0.007	0.001	0.004	0.650	0.290	0.041	0.008	0.000
Group 1/Group 3	0.112	0.001	0.002	0.015	0.000	0.001	0.028	0.496	0.970	0.001	0.000	0.000
Group 1/Group 4	0.623	0.003	0.734	0.001	0.016	0.000	0.004	0.226	0.427	0.001	0.016	0.005
Group 2/Group 3	0.326	0.326	0.028	0.545	0.001	0.791	0.910	0.427	0.762	0.019	0.003	0.019
Group 2/Group 4	0.791	0.940	0.034	0.650	0.131	0.226	0.130	0.473	0.597	0.059	0.496	0.940
Group 3/Group 4	0.545	0.496	0.000	0.405	0.016	0.596	0.226	0.112	0.649	0.059	0.028	0.082

Mann Whitney U test.

loop with whole pancreas was harvested as a sample, for histopathological confirmation of acute pancreatitis.

Biochemical analysis

Blood samples were taken for counting the blood levels of leukocyte, amylase, glucose, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT) and evaluation of acid-base status. Blood gases analysing was performed immediately with RAPIDLab248 blood gases analyser system (Siemens Healthcare, Erlingen, Germany). For further research, samples were transferred tolstanbul Training and Research Hospital, Clinical Biochemistry laboratory under appropriate conditions. Levels of serum amylase, serum SGOT, LDH, and CRP levels were measured for estimating the frequency and severity of pancreatitis by standard laboratory methods.

Histopathological examination

Pancreatic tissue samples were placed in 10% neutral formalin solution for pathological asssesment. Specimens were routinely pro-
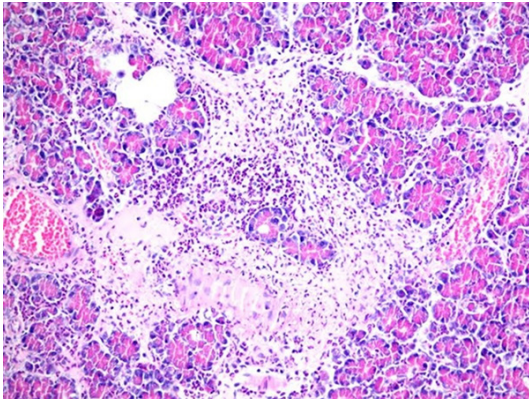
Figure 2. Hematoxylin-eosin (H-E) staining (200×). Microscopic appearance. Significant leukocyte infiltration, edema, focal fat necrosis, hemorrhage and congestion is apparent (H&E ×200).
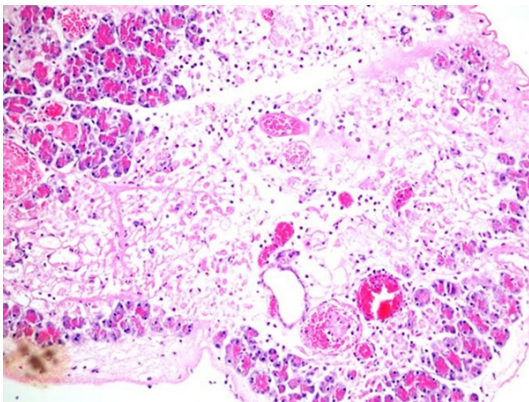

Figure 3. Hematoxylin-eosin (H-E) staining (400×). Microscopic appearance. Significant leukocyte infiltration, edema, focal fat necrosis, aciner necrosis is apparent (H&E ×400).

cessed and embedded in paraffin wax. Pancreas tissue sections of 5 μm thickness were stained with hematoxylin and eosin. The specimens were examined under light microscope as a pathologist-blinded study. Presence and grade of acute pancreatitis were evaluated and documented in each of the tissue sections according to Schmidt's method with regard to edema, acinar necrosis, hemorrhage, fat necrosis, inflammation and perivascular infiltration scores which determines the severity of acute pancreatitis described previously [8].

Statistical analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 15.0 (SPSS for Windows 15.0, Inc, Chicago, IL, USA).

The data were evaluated by descriptive statistical methods (Mean and standart deviation, Median), while intergroup comparisons were compared by Kruskal-Wallis test, and subgroup comparisons were performed with Mann Whitney U test. A '*P*' value <0.05 was accepted as statistically significant.

Results

No complication was encountered and none of the animals died during the experimental procedure. Histopathological examination of specimens revealed acute pancreatitis in all of the groups.

A homogeneous distribution was determined between the groups in means of body weight (P=0.55).

Leukocyte, glucose, SGOT, LDH, amylase, CRP, pH, PO_2, HCO_3 and base excess (BE) parameters were evaluated with Kruskal-Wallis test which showed significant difference between the groups with regard to other parameters (P<0.05), while demonstrating no significant difference between the groups in terms of platealet counts and CRP. There was a slight increase in CRP levels especially in group 3, however the difference was not statistically significant (P>0.05) (**Table 1**).

Intergroup comparision of laboratory findings

Serum levels of amylase, leukocyte, pH, HCO_3, SGOT and LDH were significantly lower in group 1 when compared to other groups (P<0.05). BE and PO_2 levels were higher in group 1 (**Table 2**).

While levels of glucose, amylase, AST, LDH were higher in group 3 than group 2, PO_2 was found to be higher in group 2.

In group 3, glucose and amylase levels were higher, PO_2 was found to be lower than group 4.

Histopathological assessment

Histopathological assessment of the specimens of the pancreatic gland were consistent with acute pancreatitis leading to interstitial edema, inflammation and perivascular infiltration, acinar necrosis, hemorrhage and fat necrosis in all experimental groups (**Figures 2**, **3**).

The difference was significant between gropus in means of acinar necrosis, inflammation and perivascular infiltration (p<0.05). Conversely,

Table 3. Mean pathological injury scores of the groups

| Injuries	Grup1 Mean ± std median	Grup2 Mean ± std median	Grup3 Mean ± std median	Grup4 Mean ± std median	KW	P value
Edema	1.95±0.59 2	2.35±0.41 2.5	3.1±0.39 3	2.6±0.21 2.5	21.156	0.000
Acinar necrosis	1.1±0.73 1	2.45±0.76 2.5	3.2±0.88 3.25	2.2±0.94 2	18.312	0.000
Hemorrhage and fat necrosis	0.95±0.59 1	0.95±0.65 1	2.05±1.03 2.25	1.15±0.62 1	7.671	0.053
Inflammation and perivascular infiltration	1±0.91 0.75	2.75±1.03 3.25	3.4±0.80 3.75	2.95±0.55 2.75	18.598	0.000

KW: Kruskal-Wallis.
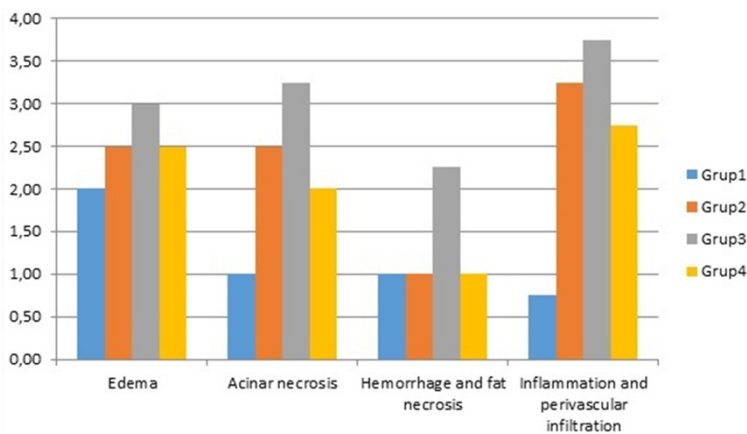
Figure 4. Comparison of the mean pathological injury scores of the groups.

Table 4. Intergroup comparison of pathological injury scores

Groups	Edema	Acinar necrosis	Hemorrhage and fat necrosis	Inflammation and perivascular infiltration
Group 1/Group 2	0.133	0.002	1.000	0.003
Group 1/Group 3	0.000	0.001	0.029	0.000
Group 1/Group 4	0.007	0.017	0.333	0.001
Group 2/Group 3	0.002	0.030	0.025	0.061
Group 2/Group 4	0.112	0.576	0.414	0.876
Group 3/Group 4	0.005	0.018	0.067	0.130

Mann Whitney U test.

there were not any significant differences in means of hemorrhage or fat necrosis (**Table 3**).

In group 2, acinar necrosis, inflammation and perivacular necrosis scores were significantly higher than group 1 (P<0.05).

All of the damage scores (edema, acinar necrosis, inflammation, perivascular infiltration) were significantly higher in group 3, when compared to group 1 (P<0.05) (**Figure 4**).

In group 3, scores of edema, acinar necrosis, hemorrhage and fat necrosis were significantly higher than group 2 (P<0.05). Similarly, edema and acinar necrosis were found to be significantly higher than group 4 (P<0.05).

In group 4, edema, necrosis, inflammation and perivascular infiltration scores were found to be significantly higher than group 1 (P<0.05). Hemorrhage and fat necrosis were found to be similar (**Table 4**).

Discussion

Although acute pancreatitis is thought to occur most often due to calculi of the gallbladder and alcohol abuse, it is a multifactorial process, starting with acinar cell damage and secretion of inflammatory mediators, which may lead to asymptomatic disease, or a life-threatening situation such as systemic inflammatory response syndrome (SIRS) or multipl organ dysfunction syndrome (MODS), caused by a cascade of reactions. It has been also reported that there may be seen life threatening attacks following ERCP, with a rate of 0-5% [9-13].

In acute pancreatitis, following acinar cell damage, amylase enters into the systemic circulation. The increase in serum level starts in 2-12 hours and reaches its peak value between 12-72 hours. Renal excretion of amylase

increases at the same time, leading to an increase in urinary concentration. In uncomplicated cases, the levels come back to normal range in a few days duration [14, 15].

Hemorrhage, cholangitis, cholecystitis, perforation and pancreatitis are among the complications of ERCP. Post-ERCP pancreatitis is suspected and diagnosed with typical pain, amylase levels 3-times higher than normal, and symptoms starting in the following 24 hours, and can be graded clinically as low, mild or serious [16].

Patient-related etiologic factors that lead to post-ERCP pancreatitis involve young females, SOD suspicion, normal bilirubin levels, previous post-ERCP or recurrent pancreatitis history, anatomic variations such as fusion anomalies of the pancreatobiliary duct, presence of anemia and history of cholecystectomy. Etiologic factors that are related with ERCP procedure are difficult cannulation, multipl attempts of cannulation, cannulation and injection of the pancreatic duct, pre-cut sphincterotomy and unexperienced endoscopist [17].

The mechanism that underlie post-ERCP pancreatitis include traumatic effect of the instrumentation of papilla and/or pancreatic sphincter, hydrostatic damage due to injection of contrast agent or saline solution, chemical and/or allergic damage caused by the injection of the contrast agent, obstruction of the pancreatic secretion due to edema or perforation casued by the thermal effect of electrosurgical unit on bile duct or ampulla [9, 18].

In previous studies, advantages of various suggestions have been reported, such as; appropriate selection of patients, preferring magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography instead of ERCP, identifying of high-risk patients before the procedure, performing guide wire cannulation instead of contrast assisted cannulation, injection of the contrast agent or saline solution at low pressures, stenting of high-risk patients and/or cases that need multipl pancreatic duct cannulations, and administration of somatostatin analogues, protease inhibitors or single dose of rectal indomethacin [11, 19]. The efficacy of stents in high-risk patients in preventing post-ERCP pancreatitis, is the deliverance of enzyme-rich pancreatic fluids away

from pancreas, without causing autodigestion. Sofuni et al. showed in their study that the rate of post-ERCP pancreatitis decreased to 3.2% from 13.6%, with stenting of the pancreatic duct [20].

In this experimental study, we evaluated the effects of direct trauma, high intraductal pressure caused by saline, chemical hazard of contrast agent on the etiology of post-ERCP pancreatitis, and compared the efficacy of washing with saline at low pressure, after the administration of contrast agent.

It is a known fact that contrast agents casue damage on the pancreas and microvascular bed in the other organs, when they are administered systemically. Conversely, in ERCP procedure, contrast agent is given directly into common biliary duct and Wirsung. Although it has been reported in the literature that contrast agents have direct hazardous effects on acinar cells [5], the occurrence of post-ERCP pancreatitis has been shown to be independent from the osmolarity of the contrast agent [21]. In our research, we performed dilutional washing with saline solution, following the direct administration of saline and contrast agent at 30 mmHg pressure into the biliopancreatic duct, to evalute this effect. In group 3, damage scores, biochemical markers and leukocyte count were found to be considerably high. The similar damage scores, biochemical findings and leukocyte count in groups 2 and 4, may be an indication of the advantageous effect of saline washing in decreasing pancreatic damage.

As an acute phase reactant, CRP level is followed in evaluating the seriousity of acute pancreatitis, with scoring systems such as Ranson and Apache [22, 23], and has been shown to be a significant indicator of the disease in various studies [24]. In our study, CRP levels were found to be significantly higher in group 3, when compared to other groups. Similarly, amylase levels were significantly lower in groups 2 and 4, than group 3. Other prognostic factor such as leukocyte, AST and LDH were similar in groups 2 and 4, lower than group 3.

All of the parameters associated with pancreatic damage were in correlation with biochemical findings, and found to be highest in group 3, similar in groups 2 and 4. With those results, as

we had aimed in our hypothesis, we have found that dilution of the contrast agent with saline solution, may be effective in decreasing the destructive results of the chemical effect. Similarly, the higher levels of damage scores in group 3 and 4 may be a predictor of the damage caused by the hydrostatic pressure of the contrast agent and saline solution, which are administered during the procedure.

In previous experimental studies concerning the effect of pressure on post-ERCP pancreatitis, it has been shown that ductal injection at high pressures cause pancreatic damage, resulting in post-ERCP pancreatitis [25].

Although post-ERCP pancreatitis is a multi-factorial, iatrogenic disease, direct traumatic damage and high pressure caused by saline and contrast agent, are important etiologic factors. In our research on experimental pancreatitis model, we have shown that dilutional effect of saline has an advantageous effect in decreasing pancreatic damage. But further prospective randomized studies with large patient groups are needed for clinical confirmation.

Conclusion

We state that further studies are necessary to confirm our findings; and carrying out laboratory and clinical studies on large patient populationsmay help defining the exact iatrogenic mechanisms resulting in pancreatitis.

Acknowledgements

Disclosure of conflict of interest

None.

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