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The effects of different mechanisms on the development of post-ERCP pancreatitis in an ERCP model in rats

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Background/aims: *To investigate the effects of different mechanisms on the development of pancreatitis after endoscopic retrograde cholangiopancreatography.* ***Material and Methods:*** *40 male rats were randomly divided into four groups. After laparotomy, in Group 1, only duodenum was reached by a 24G cannula without performing any other procedure. In Groups 2, 3, and 4, biliopancreatic duct was cannulated transduodenally. Group 2 received no additional intervention after the cannulation. Group 3 received saline, whereas Group 4 received contrast agent into the duct. After a period of 24 hours, all rats were sacrificed. Laboratory tests for blood samples were performed and pancreatic tissue was also evaluated histopathologically.* ***Results:*** *Leukocyte, blood sugar, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, amylase, C-reactive protein, and base excess parameters were evaluated. The values in Groups 2, 3, and 4 were found to be significantly higher than those in the control group, except for leukocyte count and base excess (p=0.551, p=0.031, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.683, respectively). Histopathological results demonstrated significant differences between the groups. Highest pathological damage scores were observed in Groups 3 and 4.* ***Conclusion:*** *Among different theories for the pathogenesis of post-endoscopic retrograde cholangiopancreatography pancreatitis, elevated intraductal hydrostatic pressure was observed to be the main underlying cause.*

Key words: Endoscopic retrograde cholangiopancreatography; post-endoscopic retrograde cholangiopancreatography pancreatitis, acute pancreatitis, experimental, pathogenesis

ERCP sonrası pankreatit gelişimindeki farklı mekanizmaların etkilerinin ratlardaki deneysel ERCP modelinde karşılaştırılması

Giriş ve Amaç: *Bu çalışmada endoskopik retrograd kolanjiopankreatografi sonrası pankreatit gelişiminde farklı mekanizmaların etkileri değerlendirildi.* ***Gereç ve Yöntem:*** *40 adet erkek sıçan dört gruba ayrıldı. Laparatomi sonrası, birinci grupta sadece duodenum 24G kanül ile kanüle edilip başka işlem uygulanmadı. İkinci, üçüncü ve dördüncü grupta biliyopankreatik kanal transduodenal olarak kanüle edildi. İkinci grupta kanülasyon sonrası başka işlem uygulanmadı. Üçüncü grupta salin solüsyonu, dördüncü grupta ise kontrast madde kanal içine uygulandı. 24 saat sonrasında, tüm ratlar sakrifiye edildi. Laboratuvar değerlendirme için kan örnekleri, histopatolojik değerlendirme için pankreas dokusu alındı.* ***Bulgular:*** *Lökosit, kan şekeri, serum glutamik oksaloasetikasit transaminaz, laktat dehidrogenaz, amilaz, C-reaktif protein ve baz açığı parametreleri değerlendirildi. İkinci, üçüncü ve dördüncü gruptaki değerler lökosit ve baz açığı değerleri dışındaki parametrelerde kontrol grubuna göre anlamlı ölçüde yüksekti (sırasıyla, p=0.551, p=0.031, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.683). Histopatolojik sonuçlarda gruplar arası anlamlı fark saptandı. En yüksek patolojik hasar skorları grup 3 ve 4'de elde edildi.* ***Sonuç:*** *Post-endoskopik retrograd kolanjiopankreatografi pankreatitin patogenezindeki farklı teoriler içinde, artmış intraduktal hidrostatik basınç en önemli neden gibi görünmektedir.*

Anahtar kelimeler: Endoskopik retrograd kolanjiopankreatografi, post endoskopik retrograd kolanjiopankreatografi pankreatit, akut pankreatit, deneysel, patogenez

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INTRODUCTION

Acute pancreatitis is one of the most notable complications encountered following diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP) (1). This complication occurs with a wide range of clinical profiles varying from asymptomatic elevated enzyme levels to severe pancreatitis with high mortality and has an incidence of 0-5% following ERCP, which according to various studies may reach up to 40% (2-4).

Although the mechanism behind post-ERCP pancreatitis is not well-known, various theories are discussed. However, for mechanical, chemical, hydrostatic, enzymatic, microbiological, allergic, and thermal mechanisms that are suspected of triggering pancreatitis, there is no conclusive evidence clearly demonstrating one or more of them being responsible for pancreatitis or their influence over severity of the pancreatitis (2,5).

In this study, we aim to evaluate the role and power of mechanical, hydrostatic, and chemical effects that are considered among the likely mechanisms underlying the development of post-ERCP pancreatitis.

MATERIALS and METHODS

Animals

This experimental study was conducted in the Animal Laboratory of the University of Marmara. The study was started after acquiring the approval of the hospital's ethics committee. The animals received appropriate care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals (1996) issued by the National Academy of Sciences.

We used 40 Wistar-albino male rats weighing between 370-480 g (mean weight: 410 g). The rats were kept at room temperature and fed with standard rat diet and tap water throughout the study period. The rats were randomly divided into four groups as to contain 10 rats in each and groups were designated as:

Group 1 (Control Group, n=10),

Group 2 (Cannulation Group, n=10),

Group 3 (Saline Group, n=10),

Group 4 (Contrast Agent Group, n=10).

All the experiments were carried out under general anesthesia by administration of ketamine hydrochloride 40 mg/kg and Xylazine 5 mg/kg, intraperitoneally. After testing the depth of anesthesia by checking corneal reflex and applying tail pinch technique, laparotomy was performed to each animal.

Surgical Procedure

In Group 1, following laparotomy, duodenum was reached from a point distant to the biliopancreatic duct by a 24G cannula, and the abdomen was closed without performing any other procedure.

Following application of laparotomy in Groups 2, 3, and 4, biliopancreatic duct was exposed by elevating the duodenum. After applying a small bulldog clamp to the hepatic duct, biliopancreatic duct was cannulated transduodenally by a 24G cannula for 30 seconds. Group 2 received no additional intervention after the cannulation. Group 3 received 0.5 mL saline at 30 mmHg pressure into the biliopancreatic duct, whereas Group 4 received 0.5 mL semi-dilute non-ionic contrast agent (Ultravist 300, Iopromide, Schering, Germany) at 30 mmHg pressure into the biliopancreatic duct. The fixed pressure of 30 mmHg was chosen as the most appropriate pressure value in the light of the related literature (6). Barometer of the pediatric blood pressure device was used for regulating the infusion pressure. Following surgery, the abdomen was closed with double-layer continuous sutures.

Laboratory Tests

All the rats were kept at room temperature after the procedure. Following a period of 24 hours, blood collection was carried out from the hearts by heparinized and non-heparinized syringes under ether anesthesia. Levels of leukocyte, amylase, blood sugar, lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), C-reactive protein (CRP), and blood gas were analyzed.

Histopathological Assessment

Subsequent to obtaining the blood from each rat's heart, rats were sacrificed by cervical dislocation, pancreatic tissues were removed and put into 10% formaldehyde solution and sent for pathological assessment. Histopathological assessment was performed by a single pathologist in a single-blind fashion in the pathology laboratory. The pancreatic tissues were fixated in formaldehyde and paraffin sections were prepared. The specimens were stained with hematoxylin-eosin for analysis under light microscopy and evaluated according to the Schmidt's method with regard to edema, acinar necrosis, hemorrhage, fat necrosis, inflamma-

tion, and perivascular infiltration by a scoring system between 0-4 (7).

Statistical Analyses

Statistical analyses were carried out by GraphPad Prism v.3 package program. The data were evaluated by descriptive statistical methods (Mean, Standard Deviation), while intergroup comparisons were conducted by Kruskal-Wallis test, and subgroup comparisons were performed with Dunn's multiple comparison test. $p<0.05$ was recognized as statistically significant.

RESULTS

The groups had a homogeneous distribution with regard to weight (p=0.687). Leukocyte, blood sugar, SGOT, LDH, amylase, CRP, and base excess (BE) parameters were evaluated with Kruskal-Wallis test which showed no significant difference between the groups in terms of leukocyte count and BE, while demonstrating a significant difference between the groups with regard to other parameters (Table 1). The diagnostic parameters for pancreatitis showing a significant difference between the groups were evaluated with Dunn's multiple comparison test (Table 2), i.e. amylase and CRP levels in the cannulation group were significantly higher than those in the control group. However, the values in this group were significantly lower than those in Groups 3 and 4. The values in Groups 2, 3, and 4 were found to be significantly higher than those in the control group, whereas the highest values were encountered in Groups 3 and 4.

The analysis of pathological results by Kruskal-Wallis test demonstrated significant differences between the groups (Table 3). Regarding the histopathological damage scores, the edema, acinar necrosis, inflammatory infiltrate, and perivascular infiltration values in our study were consistent with the results of the blood parameters. Those parameters were further evaluated by Dunn's multiple comparison test (Table 4). Highest pathological damage scores were observed in Groups 3 and 4, but the difference was not statistically significant (Figure 1).

DISCUSSION

The influence of multiple factors in the mechanism of pancreatitis development after ERCP is an ongoing focus of discussion. In this study, we performed a comparative analysis on the mechanical damage caused by direct papillary trauma, elevated intraductal hydrostatic pressure induced by saline, and the chemical influence of the contrast agent.

Table 1. Mean laboratory blood values of the groups

	Group 1	Group 2	Group 3	Group 4	KW	*P*
Leukocyte	7310±2633,31	8200±2330,47	8570±2346,18	8130±1202,82	2,10	0,551
Blood sugar	137,8±6,76	132,9±8,67	147±10,59	135±14,34	8,87	0,031
SGOT	281,6±99,47	394±89,09	659±255,28	808±450,92	22,55	0,0001
LDH	1379,6±486,09	2644±438,34	3170±926,97	3455±1777,02	18,38	0,0001
Amylase	2386±745,49	4113±1884,21	7166±3988,87	9418±6463,45	25,14	0,0001
CRP	298,5±75,3	530±76,09	940,9±285,52	1431,1±121,44	35	0,0001
Base excess	-0,85±2,41	-1,58±3,3	-1,95±4,13	-2,86±4,16	1,50	0,683

KW: Kruskal-Wallis. SGOT: Serum glutamic oxaloasetic transaminase. LDH: Lactate dehydrogenase. CRP: C-reactive protein.

Table 2. Intergroup comparison of blood analysis

	Blood Sugar	SGOT	LDH	Amylase	CRP
Group 1 / Group 2	0,14	0,015	0,0001	0,007	0,0001
Group 1 / Group 3	0,024	0,001	0,0001	0,0001	0,0001
Group 1 / Group 4	0,579	0,001	0,003	0,0001	0,0001
Group 2 / Group 3	0,015	0,003	0,174	0,031	0,0001
Group 2 / Group 4	0,49	0,007	0,364	0,002	0,0001
Group 3 / Group 4	0,042	0,596	0,762	0,212	0,003

SGOT: Serum glutamic oxaloasetic transaminase. LDH: Lactate dehydrogenase. CRP: C-reactive protein.

Table 3. Mean pathological injury scores of the groups

	Group 1	Group 2	Group 3	Group 4	KW	*P*
Edema	0,2±0,35	1,05±0,5	2,1±0,62	2,5±0,53	30,77	0,0001
Acinar necrosis	0,05±0,16	0,55±0,37	1,35±0,58	1,4±0,46	27,65	0,0001
Inflammation	0,2±0,26	0,9±0,39	1,55±0,6	2,05±0,5	28,98	0,0001
Hemorrhage	0,1±0,21	0,7±0,54	0,9±0,57	0,85±0,53	14,82	0,002
Fat necrosis	0,05±0,16	0,3±0,35	0,7±0,67	1,95±0,98	24,96	0,0001
Perivascular infiltration	0,1±0,21	0,55±0,5	1,5±0,62	1,55±0,55	25,93	0,0001

KW: Kruskal-Wallis

Table 4. Intergroup comparison of pathological injury scores

	Edema	Acinar Necrosis	Inflammation	Hemorrhage	Fat Necrosis	Perivascular Infiltration
Group 1/Group 2	0,001	0,002	0,001	0,005	0,053	0,019
Group 1/Group 3	0,0001	0,0001	0,0001	0,001	0,006	0,0001
Group 1/Group 4	0,0001	0,0001	0,0001	0,001	0,0001	0,0001
Group 2/Group 3	0,002	0,005	0,016	0,432	0,161	0,003
Group 2/Group 4	0,0001	0,001	0,0001	0,527	0,0001	0,002
Group 3/Group 4	0,139	0,906	0,077	0,841	0,005	0,812

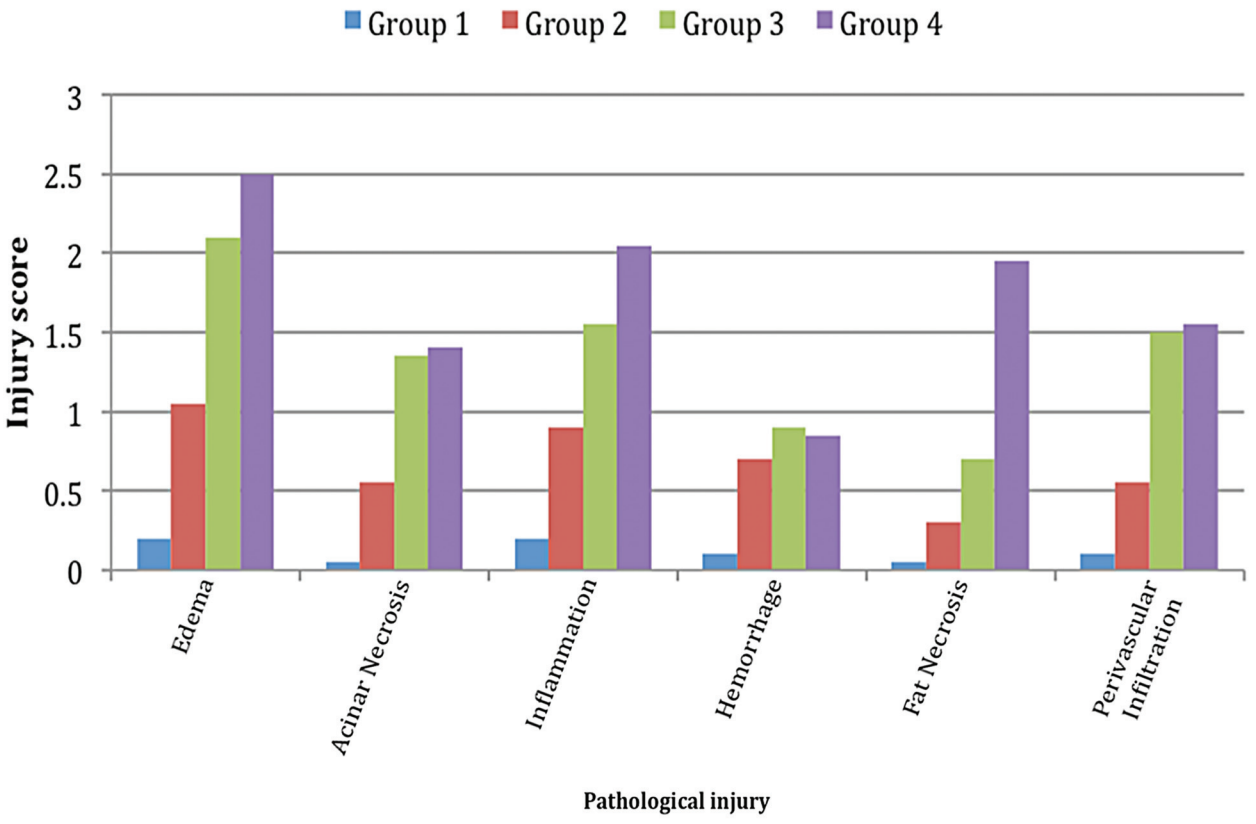

Figure 1. Comparison of the mean pathological injury scores of the groups.

Secretion of amylase from inflamed pancreas and its serum levels, the indicator used for pancreatitis diagnosis, demonstrate an increase during the early periods of acute pancreatitis. This increase begins 2-12 hours after the start of the acute pancreatitis episode and occurrence of the clinical symptoms, attains the peak level at 12-72 hours and generally returns to normal levels within one week in cases with no complications (8,9). The most important acute phase reactant that is frequently employed in the assessment of the severity of acute pancreatitis and extent of the current inflammation is CRP. Many clinical studies focusing on CRP levels in acute pancreatitis cases have demonstrated a significant CRP increase. Those studies show that as the Ranson and Apache score, which is used for clinical assessment of acute pancreatitis, increases, CRP level rises as well (10-12). Those two parameters (amylase and CRP) are most commonly used in the establishment of pancreatitis diagnosis and assessment of its severity. In our study, amylase and CRP levels in the cannulation group were significantly higher than those in the control group. However, the values in this group were significantly lower than those in Groups 3 and 4. Similarly, the values in Groups 3 and 4 were significantly higher than those in the control group. While there was no difference between Group 3 and 4 with regard to amylase value, Group 4 had the highest CRP value. Serum LDH and SGOT levels are two of the other prognostic criteria deployed for determination of acute pancreatitis (13). The values in Groups 2, 3, and 4 were significantly higher than those in the control group, whereas LDH values in Groups 2, 3, and 4 along with SGOT values in Groups 3 and 4 were not significantly different.

Regarding the histopathological damage scores, the edema, acinar necrosis, inflammatory infiltrate and perivascular infiltration values in our study were consistent with the results of the blood parameters. While the pathological response in Groups 2, 3 and 4 was significantly higher than that in the control group, it was statistically significantly different in Groups 3 and 4 than in Group 2. Despite acquiring higher scores in Group 4 than in Group 3, this difference was not statistically significant. Pathological assessment revealed no significant difference between Groups 2, 3, and 4, whereas fat necrosis was severe particularly in Group 4.

Both sphincter of Oddi spasm and/or edematous hemorrhagic papilla induced by endoscopically direct trauma lead to pancreatic edema and pancreatitis by reducing the flow rate of pancreatic fluid (14-16). Based on this theory, treatments aiming at decreasing the pressure in sphincter of Oddi have been started for reducing the post-ERCP pancreatitis risk. Recently, although nifedipine, glyceryl trinitrate (GTN), topical epinephrine or botulinum toxin have been used for this purpose, the results appear to be contradictory with each other (17-22). GTN, the most promising one among those, is a rapid-acting short-standing nitric oxide source that considerably decreases the sphincter of Oddi pressure, which is used in cardiovascular diseases. Sudhindran et al. conducted a randomized study by comparing placebo and sublingual nitrate in which they found lower pancreatitis risk in the nitrate group compared with the control group (8%-18%) (17). Similarly, Moreto et al. performed a randomized study where they applied placebo and transdermal GTN, and found lower pancreatitis rate in the GTN group (4%-15%) (18). However, high pancreatitis rates in the control groups of those two studies have been a focus of discussion. In the similar study of Kaffes et al., GTS was found to have no influence over prevention of post-ERCP pancreatitis (7.7%, 7.4%) (23). Botulinum toxin is another agent used for this purpose. Sand et al. conducted an experimental study and observed that it reduced the resting pressure of the sphincter of Oddi (24). In the studies of Gorelick et al. and Wehrman et al., botulinum toxin was found to reduce the post-ERCP pancreatitis rate by decreasing the residual pancreatic sphincter hypertension among patients with Oddi dysfunction (19,25). By this study in which post-ERCP pancreatitis rate was reduced by decreasing the Oddi spasm, elevated intraductal pressure was found to play a role in the pathogenesis, which was a finding consistent with the results of our study. Group 2, when compared with the control group, demonstrated development of pancreatitis, however, the damage was more limited compared with the Groups 3 and 4 with regard to blood parameters and pathological response.

Both forces increasing the hydrostatic pressure such as infusion of a fluid into the pancreatic duct and injection pressure applied during the infusion, lead to ductal, epithelial, and acinar damage. These damages occur as a result of the disruption of tight junctions due to retrograde flow of intraductal content (2,26). In the present study, by applying a fixed injection pressure (30 mmHg) on the

rats of Group 3 and 4, we eliminated the injection pressure variable out of the equation. Data acquired from both Group 3 and Group 4 demonstrated development of pancreatitis, and pancreatitis was observed to be more severe in those groups than in Groups 1 and 2. Amylase, SGOT and CRP values were significantly higher in Groups 3 and 4, while histopathological assessment revealed significantly higher edema, acinar necrosis, inflammatory infiltrate, and perivascular infiltration scores. Haciahmetoglu et al. conducted a study focusing on the effects of different injection pressures over development of pancreatitis, and the comparison with the study groups and the control group exhibited a significantly higher CRP, SGOT, and LDH values in ductal injection groups. Pathological assessment revealed no significant pathological change in groups subjected to low pressure, however, significant pathological changes were observed as the pressure increased (27). In the current study, we observed that increasing of the pressure is effective for the development of the pancreatitis in Groups 3 and 4 when compared with Groups 1 and 2. Another theory supporting the hydrostatic pressure elevation mechanism involves pancreatic stents used for prevention of post-ERCP pancreatitis. As in all other prophylactic methods used for this purpose, stents are employed for inhibiting the intrapancreatic inflammatory cascade at some point. Although it is not known by which mechanism it achieves that purpose, it is thought to facilitate the removal of activated enzyme-rich fluid, which leads the intraductal pressure to drop following the procedure (28). In the randomized study by Sofuni et al. on 201 patients, pancreatitis rate in the pancreatic stent group (3.2%) was found to be significantly lower than the rate in the non-stent group (13.6%) (30). Various studies have exhibited similar results (30-32).

Contrast agents used in pancreatography are known to aggravate pancreatitis by direct chemical toxic influence (2,33). Bub et al. conducted an experimental study and demonstrated the morphological changes in the epithelial tissue of the pancreatic duct induced by contrast medium (34). Similarly, Kivisaari showed developing of the edema, atrophy, and fibrotic changes in the pancreatic tissue after the retrograde injection of the contrast medium (35). Since particularly high osmolarity and ionic content are thought to act as major factors in formation of this pancreatic damage, non-ionic contrast agents with low osmolarity are preferred lately. However, George et al. performed a meta-analysis and found no difference between the high and low osmolarity with regard to development of post-ERCP pancreatitis (36). In the present study, we used iopromide as the non-ionic contrast agent in Group 4. In view of the results, pancreatitis was observed to develop in this group as well, however, blood parameters and pathological findings were not significantly different than those in Group 3. Only CRP value and fat necrosis score were significantly higher compared with the Group 3. These results showed that administration of contrast agent does not have any additional effect on either the development of pancreatitis or the severity of pancreatitis.

In conclusion, among different theories on pathogenesis of post-ERCP pancreatitis which is known to be of multifactorial etiology, mechanical effect of Oddi spasm induced by cannulation initiates the development of pancreatitis however does not increase its severity. The direct toxic effect of administered contrast agent was found to be low, whereas elevated intraductal hydrostatic pressure due to saline or contrast agent was observed to be the main underlying cause. Further prospective and randomized clinical studies including larger series will be beneficial in both revealing the true etiology of the condition and implementing the novel and effective prophylactic methods into current clinical practice.

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