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Risk of Post-ERCP Pancreatitis in Liver Transplant Patients: Single Center Experience

Shailender Singh
University of Nebraska Medical Center

RISK OF POST-ERCP PANCREATITIS IN LIVER TRANSPLANT PATIENTS: SINGLE CENTER EXPERIENCE

by

Shailender Singh, MD

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Advisory Committee:
Surinder K. Batra, Ph.D.
Apar K. Ganti, M.D.
Lani Zimmerman, Ph.D.

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Abstract:

Introduction: Acute pancreatitis remains the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP). The exact cause of post-ERCP pancreatitis (PEP) is unclear. Regardless of the mechanism that initiates PEP, the pathways of inflammation are similar to other forms of acute pancreatitis and include the activation of various inflammatory cytokines, released from the acinar cells and subsequently from helper T lymphocytes and macrophages. Liver transplants (LTx) patients on immunosuppressive medications have impaired T-cell response and hence decreased ability to generate these cytokines. The aim of this study was to review incidence rates and risk factors of PEP in this LTx subset of patient population compared to non transplant (non-LTx) patients.

Methods: Retrospective review of liver transplant database from January 2005 to September 2015 was performed. Liver transplant patients who underwent ERCP in the post-transplant period as part of their usual management were included in the study and compared with non-LTX patients who underwent ERCP. The study was approved by IRB. Electronic medical records were reviewed for any mention of pancreatic-type pain and pancreatic enzyme testing, if any after the ERCP. Diagnosis of Post-ERCP pancreatitis was made on the basis of both clinical and laboratory results as per standard definitions of PEP.

Results: During this period, 109 LTx patients underwent 235 ERCP procedures. The data was compared with 348 non-transplant patients (not on any immunosuppression) who underwent total of 536 ERCP procedures. PEP developed in 24 (4.47%) cases in the non-LTx group as compared to 4 (1.7%) cases in the LTx group ($p = 0.061$, OR 2.70). History

of LTx showed trend towards decrease in risk of PEP on univariate analysis (OR 0.36, p = 0.068, 95% CI = 0.12 - 1.07). However, on multivariate analysis only female gender (OR 2.35, P < 0.038, CI 1.04 - 5.28), history of PEP (OR 5.77, P < 0.001, CI 2.01 - 16.55) and pancreatic duct contrast injection (OR 6.20, P < 0.001 CI 2.75 - 13.97) were significantly associated with risk of PEP. Also the severity of pancreatitis was mild in all 4 LTx patients as compared to 21 out of 24 patients (87%) with mild PEP in the non-LTx group (p <0.001).

Conclusion: The risk of PEP in liver transplant patients on immunosuppression appears lower than the historical risk. Inhibition of the inflammatory transcriptional factors such as NF-κB and NFAT by the calcineurin inhibitors may be a potential explanation. Further studies are needed targeting calcineurin activation as a therapeutic approach in prevention of PEP.

Introduction:

Biliary tract complications occur in 5% to 25% of patients after liver transplantation.(1-4) These complications include biliary strictures, bile leaks, choledocholithiasis, biliary casts, biloma, and hemobilia. Bile duct anastomotic strictures are quite common and affect 15% to 20% of patients after deceased OLT and 19% to 40% after living donor liver transplantation.(5) ERCP is the preferred initial treatment choice because it helps to confirm the diagnosis and allows therapy.(6-9) The reported complication rates for ERCP in the general population vary between 4% and 12% (10-14) though the most frequent and feared complication of ERCP is post-ERCP pancreatitis (PEP), which is associated with significant post procedure morbidity and mortality. The incidence of PEP reported in the literature ranges from 1% to 30% of all procedures, the frequency depending on different patient and procedure related variables. Rates of pancreatitis of 2% to 9% are typical of most unselected prospective series.(15) Published series of LTx recipients who underwent ERCP for biliary complications indicate that the risks of bleeding, pancreatitis, and cholangitis, among other complications, after the procedure range between 2% and 18%.(16-19) Nonetheless, the specific risks of PEP in LTx recipients have not been well studied, and there are limited data on the complications of this procedure in this patient population. Although procedure-related factors play a role in the development of these complications, patient-related factors likely play a relevant role in this population, given the fact that LTx recipients receive long-term immunosuppression. In addition, prior studies did not specifically evaluate the procedure related risk factors for PEP in this patient population. These patients are on long-term immunosuppression and the effects of these medications on PEP rates are unknown. PEP, being an immune mediated inflammatory process, and LTx patients are on immunosuppression, **we hypothesize the risk of PEP in this LTx population is**

different than the risk in general population. The purpose of this study was to examine the incidence, specific risk factors of PEP complications in LTx patients. Secondary aim was to determine the severity of PEP in LTx patients.

Material and methods:

This study was conducted at University of Nebraska Medical Center. The institutional review board approved the study protocol. Retrospective review of liver transplant database from January 2005 to September 2015 was performed. Adult liver transplant patients who underwent ERCP in the post-transplant period as part of their usual management were included in the study. The patients were identified by searching the transplant database using procedure codes for ERCP. The Medical records of selected patients were retrospectively reviewed and both patient and procedure related potential variables were collected. The procedures were performed by the university academic faculty. Management of the ERCP findings i.e. choice of biliary stents for findings of anastomotic stricture or bile leak was as per the discretion of the endoscopist. Difficult biliary cannulation was recorded as per the description in the procedure report i.e. multiple attempts to cannulate CBD or pre-cut sphincterotomy done. Antibiotics were given to patients with evidence of infection or if complete biliary drainage could not be attained. Pharmacological prophylaxis with rectal indomethacin and/or pancreatic stent placement for PEP prophylaxis was performed as per the discretion of the endoscopist. At our institution, sedation for the ERCP is provided by anesthesiologist and patients are routinely discharged after the procedure unless clinical situation dictates otherwise. To identify the development of PEP, the electronic medical records were reviewed for any mention of pancreatic-type pain and pancreatic enzyme testing, if any within 3 days of the procedure date. Data regarding the indication for ERCP, patient related factors like age and gender, prior history of PEP and therapeutic procedures during ERCP such as

sphincterotomy, precut sphincterotomy, difficult cannulation, biliary stricture dilation, biliary stent placement, stone extraction, PD cannulation and PD stenting were evaluated and collected in database.

Definition of findings

Post ERCP pancreatitis (outcome variable): The diagnosis of PEP was made when there was documentation in the electronic record of at least 2 of 3 diagnostic criteria (typical pancreatic abdominal pain, elevated amylase and/or lipase levels, and pancreatic inflammation on cross-sectional imaging) were present within 72 hours of the ERCP procedure. The severity of PEP was defined according to criteria previously established by Cotton et al.(20) The severity was based mainly on the need for hospitalization. Mild events were considered when hospitalization was prolonged by 2 to 3 days, moderate by 4 to 10 days, and severe by more than 10 days. Fatal events were considered when death was attributable to the procedure. **Difficult cannulation:** This was recorded as described per the endoscopist report, needed pancreatic duct (PD) stent placement to gain biliary access or via precut cannulation. **Immunosuppression protocol:** Standard immunosuppression in our center includes administration of tacrolimus or cyclosporine and prednisone. The dose of immunosuppression was managed by our institute transplant team as per the clinical protocol.

Statistical analysis

Sample size: Sample size was calculated a priori using an α=0.05 (Type I error) and β=0.2 (Type II error). The incidence of post-ERCP pancreatitis in general population was assumed at 8% and in post LTx population was assumed to be about 2.5% based on

previous literature. This yielded a sample size of 514. Some patients had more than one ERCP procedure, however, the procedure and its complications were considered as independent observations for data analysis. Continuous variables were summarized as means and standard deviations or medians and range. Categorical variables were compared by using the χ^2 or the Fisher exact test when appropriate. Continuous variables were compared by using the Student 2-tailed *t* test. The established risk factors for PEP were evaluated in univariate analysis. Risk factors for PEP with P<0.15 in univariate analysis were evaluated with multivariate logistic regression techniques using backward stepwise elimination approach. Multivariate logistic regression analysis determined those variables independently associated with PEP, after adjusting for other variables. Associations are specified as odds ratio (OR) with a 95% confidence interval. A 2-sided probability value <0.05 was considered to be significant. Statistical analysis was performed by using SAS 9.4.

Results

From January 2005 to September 2015, a total of 235 ERCP procedures were performed on 109 LTx patients and 536 procedures performed in 348 non-LTx patients. Characteristics of ERCP procedure between the 2 groups is shown in table 1. In the LTx group, the mean age of patients was 52.73 years (74 males and 35 females). Indications of ERCP procedure in the LTx patients were: abnormal LFT's = 110, bile leak = 44, anastomotic stricture = 27, stent removal = 52, pancreatic fistula = 1, choledocholithiasis = 1. In the non-LTx group there were 536 ERCP procedures performed (348 patients, 175 males and 173 females), mean age was 55.68 years, more than the mean age in LTX group (P = 0.004). Indications of ERCP in the non-LTx group: bile duct stone = 53, bile leak = 31. Pancreatic duct leak 15, bile duct stricture = 8, abdominal pain = 39, chronic

pancreatitis = 72, abnormal abdominal imaging 17, abnormal liver tests = 163, acute pancreatitis = 43, ampullary mass = 7, cholangitis = 16, cholangiocarcinoma = 9, stent follow up = 22, others = 41.

Procedure related factors which are known to increase the risk of PEP were reviewed. Among them, biliary pre-cut sphincterotomy, CBD pneumatic dilation and difficult cannulation were not significantly different between the two groups. However, other high risk factors for PEP such as biliary sphincterotomy ($p = 0.0002$), pancreatic duct cannulation ($p = 0.0001$), pancreatic duct contrast injection ($p = 0.012$), pancreatic sphincterotomy ($p < 0.0001$) were more in non-LTx group. Intervention such as pancreatic duct stent placement, known to be protective for PEP were performed more in the non-LTx group ($p < 0.0001$). In the non-LTx group, there were more patients with prior history of PEP (30 compared to 1 instance of PEP in the LTx group, $p = 0.0002$).

Characteristics of patients who developed PEP are shown in table 2. PEP developed in 24 (4.47%) cases in the non-LTx group as compared to 4 (1.7%) cases in the LTx group ($p = 0.061$, OR 2.70). Procedure related factors for increased risk of PEP (biliary sphincterotomy, pancreatic duct cannulation, pancreatic duct contrast injection, pancreatic sphincterotomy) were not statistically different between the two groups who developed PEP. Procedure related factor known to be protective for PEP i.e. pancreatic duct stent placement was performed in 13 patients in the non-LTx group as compared to none in the LTx group. Patient related factors such as age and gender were similar in both groups. The only different patient related factor is use of immunosuppression medications in the transplant group. Also the severity of pancreatitis was mild 87% in non-LTx group vs 100% in the transplant group assessed as per criteria of Cotton classification ($p = 0.0017$).

Univariate and multivariate logistic regression analyses were performed for the outcome of PEP among all patients. The univariate analysis (Table 3) showed an increased risk of PEP in cases where pancreatic interventions occurred such as PD stenting, pancreatic sphincterotomy, pancreatic duct contrast injections and PD cannulation. PEP was also significantly more in patients with prior history of PEP (OR 7.8, 95% CI = 2.91 - 20.98). Among patients with LTx, the risk of PEP was lower but not statistically significant (OR 0.36, p = 0.068, 95% CI = 0.12 - 1.07). Multivariate logistic regression (Table 4) was performed after including only those variables in the analysis those had $p<0.15$ on univariate regression and then using a backward stepwise elimination approach to find the model that was the best fit. On multivariate analysis, female gender, prior history of PEP and only PD contrast injection were significantly associated with risk of PEP.

Discussion: Acute pancreatitis is the most common complication of ERCP, a procedure performed for various pancreato-biliary disorders. About 700,000 ERCP procedures are performed annually in the United States. With its inherent complication risk, PEP represents a substantial cause of morbidity and mortality. The causes of the initiating events of PEP during ERCP are not well understood. Some of the proposed causes include: mechanical obstruction of the papilla/pancreatic duct by edema/injury due to instrumentation, thermal injury from electrocautery, hydrostatic injury from the injection of contrast, or chemical or allergic injury from contrast injection. Regardless of the inciting cause of acute pancreatitis, the initial events occur at the level of acinar cells and one of the earliest event is rise in cytosolic calcium leading to activation of several signaling pathways. One of the targets of pathologic calcium rise is the Ca^{2+}/calmodulin dependent serine/threonine phosphatase calcineurin. It is well established that the calcineurin-dependent transcription factor, nuclear factor of activated T cells (NFATc) regulates trypsinogen activation, inflammation, and pancreatic tissue damage in AP.(21) In this study, they demonstrated that the activation of trypsinogen by secretagogues in acinar cells was prevented by pharmacologic inhibition of NFAT. Importantly, only calcineurin is known to activate the NFAT transcription factors thereby controlling the expression of several genes (e.g. genes for cytokines such as IL-2, IL-4 and IFNγ). FK-506, a calcineurin inhibitor has been shown to impair protease activation in pancreatic acinar cells and protects against mild pancreatitis in vivo.(22, 23) In addition to its ability to inhibit NFAT activation, FK-506 can also inhibit the NF-κB pathway by blocking translocation of c-Rel from the cytoplasm to the nucleus, inhibit IL-2 production at the transcriptional level and decrease the local and systemic severity in acute pancreatitis.(21, 24, 25) In our preliminary studies we have also demonstrated protective effect of FK-506 in acute experimental pancreatitis. There was significant difference in histology scores and cytokine profile of animals treated with FK-506 prior to induction of pancreatitis as

compared to control animals (Figure 2 and 3). On similar lines, there was decreased production of pro-inflammatory cytokines (α-TNF, IL-1, IL-6) and increase in anti-inflammatory IL-10 in animals treated with FK-506 (Figure 4). In addition, clinically, there are reports of decreased incidence of PEP in patients who are taking FK-506 for organ transplantation.(18, 26) FK-506 is routinely used in clinical practice for immunosuppression after liver transplantation and has favorable clinical profile.

The results of this analysis specifically looked at risk of PEP in liver transplant recipients on immunosuppression. The findings in this study show that in LTx patients the frequency of PEP is 1.7%, lower than the non-LTx group (P = 0.068). The risk of PEP in our non-Tx group of 4.47% is comparable to reported rates of 4-12% in the general non-LTx population. In our non-LTx cohort, there were significantly more procedure related risk factors for PEP such as biliary sphincterotomy, pancreatic duct cannulation, contrast injection and pancreatic sphincterotomy. 1.7% risk of PEP among LTx patients in our study is similar to results of our recent meta-analysis of risk of PEP among LTx patients (abstract ID: 343432, ACG 2017). Among 61 studies of ERCP in LTx patients, there were 7,730 ERCP procedures performed on 3,980 patients, with 183 instances of PEP. The overall percentage of procedures with PEP, as estimated from our meta-analysis is 1.53% (95% CI: 0.90% - 2.28%). Forest plot (Fig. 1) shows all the studies included in our meta-analysis with number of ERCP procedures and incidence of PEP. The results of the meta-analysis and this current study indicate that the risk of PEP in LTx patients appear to be lower than the risk in general population.

An important finding of our study is that, among the procedure related risk factors of PEP, only pancreatic duct contrast injection was significantly associated with PEP after adjusting for other variables. This is in line with recent mechanistic evidence of pancreatitis being induced by the radiocontast dye, which is used in ERCP. Sohail et al(27) have

demonstrated that incubation of mouse and human acinar cells with the radiocontrast dye (iohexol) led to increase in cytoplasmic calcium, activation of the transcription factors NF-kB and nuclear factor of activated T cells. Suppressing Calcium signaling or calcineurin with FK506 prevented activation of NFkB and acinar cell injury. They also showed that calcineurin deficient mice were protected against induction of pancreatic inflammation by the radiocontrast dye. This is consistent with clinical data that show that risk of PEP can be decreased by pancreatic duct stenting to relieve ductal pressure, as well as by minimal contrast injection.(28, 29) However, placing pancreatic duct stent can be technically challenging in general practice and often is unsuccessful.

The study has a few limitations. Being retrospective review, there may be inconsistencies in the description of the procedure findings and reporting. As an example number of biliary sphincterotomies, 261 in 348 non-LTx patients and 80 in 109 in LTx group appear lower than would be expected. Procedure related predictor variables such as difficult cannulation and amount of pancreatic duct contrast injection are not standardized. It is possible that some patients may have been admitted to outside hospitals for PEP and the complication was not recorded in their medical record here at our institution. The relationship between risk factor of pancreatic duct contrast injection and PEP may be affected since there is lack of accurate description about amount of pancreatic duct contrast injection leading to acinarization or not. Another limitation is about the exact immunosuppression regimen of the transplant patients, serum levels of FK-506 were not available. FK-506 is the standard immunosuppression regimen and majority of the patients were on it. However, we were unable to obtain exact medications, with or without steroids and/or concomitant sirolimus at the time of the procedure. The role of steroids in prevention of PEP is controversial with studies reporting favorable effect(30) and no benefit.(31) The effect of steroids in pancreatitis is certainly plausible due to it

mechanistic properties, for example the inhibition of phospholipase A2, causing increase functional C1 esterase inhibitor levels. C1 esterase inhibitor is a protease known to suppress trypsin activation, a key process in acute pancreatitis. The effect if any of rectal indomethacin could not be reviewed in our study. Majority of procedures were performed before the widespread use of rectal indomethacin and its use is left to the discretion of the endoscopist. In the seminal study which showed benefit, in high risk patients rectal indomethacin along with pancreatic duct stenting reduced the risk of PEP from 16.1% to 9.7% (P = 0.04).(32) In addition, in a randomized controlled study of consecutive patients undergoing ERCP, rectal indomethacin did not prevent post-ERCP pancreatitis.(33)

Conclusions: Several signaling pathways are simultaneously activated in AP. Attempts at pharmco-prevention of PEP targeting single pathway have been largely unsuccessful, owing largely due to “compensation” and redundancy in immune response. Identifying and targeting the “initiating event” in acute pancreatitis may be more beneficial rather than preventing “inflammation” once it has been started. Mechanistically, rise of intracellular calcium in acute pancreatitis is accepted as the first event after the injurious stimuli and Ca^{2+}/calmodulin-dependent phosphatase calcineurin has been shown to be an important target of this pathologic rise in acinar cell calcium. Our study provides some clinical data suggesting that use of calcineurin inhibitors may retard calcium mediated processes and thus prevent PEP. Further studies are needed to investigate its mechanism and efficacy in prevention of PEP.

Table 1: Baseline characteristics of ERCP procedure of participants

No of procedures	Non-LTx (n=536)	LTx (n =235)	P value
Age (yrs)	55.68	52.73	0.004
Gender	Male 278	Male 156	0.001
	Female 258	Female 79	
History of Post-ERCP Pancreatitis	30	1	0.001
Therapeutic intervention at each ERCP, no (%)			
Biliary Sphincterotomy	261	80	0.001
Biliary Precut Sphincterotomy	14	8	0.638
CBD pneumatic dilation	48	23	0.696
Biliary stent placement	189	140	0.001
Difficult Cannulation	68	35	0.421
Pancreatic duct cannulation	181	47	0.001
Pancreatic duct contrast Injection	138	41	0.012
Pancreatic stent placement	121	16	0.001
Pancreatic sphincterotomy	52	0	0.001
Unsuccessful procedure	21	7	0.676
Post-ERCP pancreatitis	24 (4.47%)	4 (1.70)	0.061

Table 2: Characteristics of patients who developed PEP

	Non-LTx group (24)	LTx group (4)	p-value
Age (yrs)	52.4	48	0.681
Gender	Male 8	Male 3	
	Female 16	Female 1	0.269
History of PEP	6	1	1
Biliary Sphincterotomy	13	1	0.595
Biliary Precut Sphincterotomy	0	0	1
CBD pneumatic dilation	1	0	1
Biliary stent placement	6	3	0.084
Difficult Cannulation	4	2	0.191
Pancreatic duct cannulation	18	2	0.554
PD contrast Injection	16	2	0.601
Pancreatic stent placement	13	0	0.101
Pancreatic sphincterotomy	7	0	0.545
Severity of Pancreatitis	21 mild, 3 moderate	4 mild	0.001
Immunosuppression	0	4	0.001

Table 3: Univariate analysis for the risk of PEP

	Odds ratio	P value	[95% Conf. Interval]
Liver Transplant	0.36	0.068	0.12 - 1.07
PD stent	4.32	0.001	2.00 - 9.31
PD sphincterotomy	5.17	0.001	2.08 - 12.80
PD injection	6.50	0.001	2.94 - 14.37
PD entered	6.43	0.001	2.78 - 14.82
Amp Balloon Dilation	0.35	0.314	0.04 - 2.66
CBD Stent	0.62	0.250	0.27 - 1.39
CBD sphincterotomy	1.27	0.532	0.59 - 2.70
Difficult cannulation	2.24	0.072	0.93 - 5.42
History of PEP	7.82	0.001	2.91 - 20.98
Gender (females)	2.04	0.070	0.94 - 4.42
Age group*	0.41	0.038	0.18 - 0.95

*age group: <=56 or >56 (56 years is the median)

Table 4: Multivariate logistic regression for risk of PEP

	Odds ratio	P value	[95% Conf. Interval]
PD injection	5.77	0.001	2.75 - 13.97
History of PEP	5.77	0.001	2.01 - 16.55
Gender (F)	2.35	0.038	1.04 - 5.28

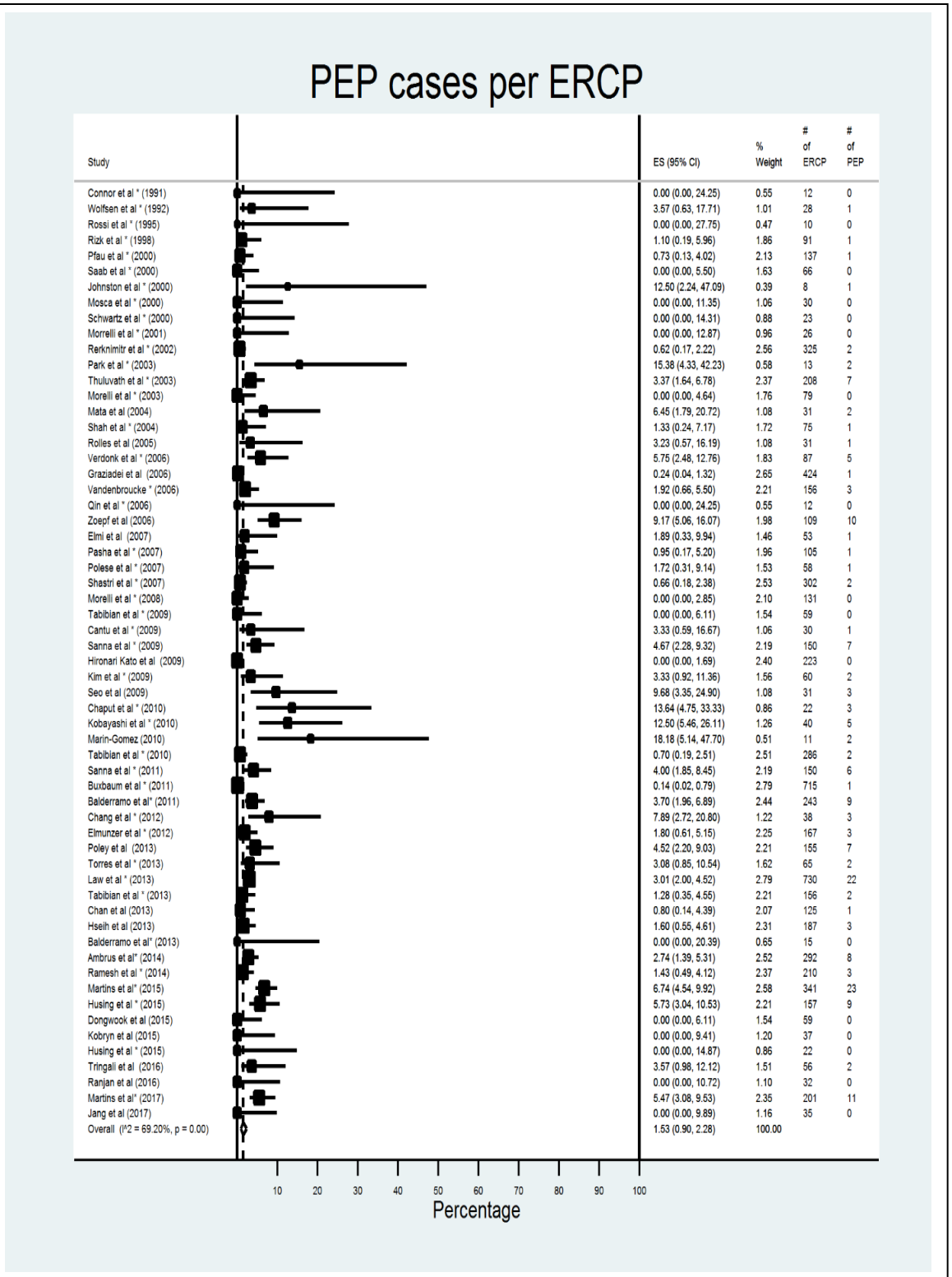

Figure 1: Studies of ERCP performed in LTx patients and risk of PEP

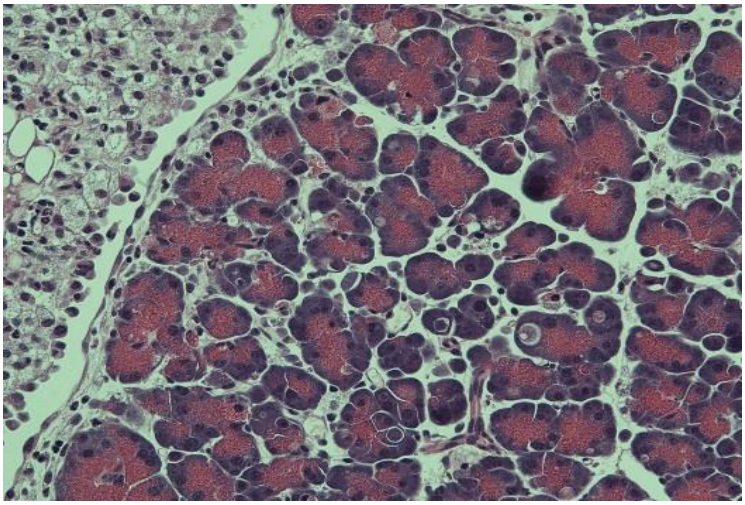

Figure 2: H&E staining of control pancreatitis with tissue edema and neutrophil infiltration

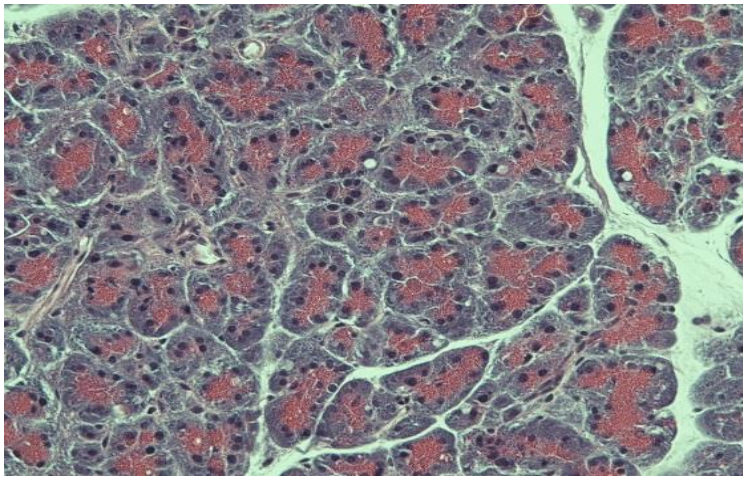

Figure 3: H&E stain of pancreas showing less edema and less infiltration with FK-506 therapy

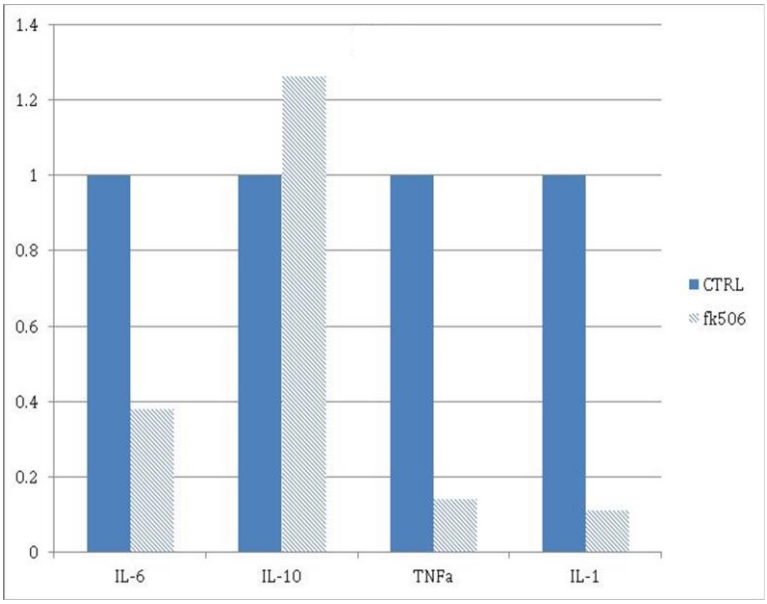

Figure 4: Cytokine profile with FK-506 intervention experimental pancreatitis

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