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ORIGINAL ARTICLE

Change in serum levels of inflammatory markers reflects response of percutaneous catheter drainage in symptomatic fluid collections in patients with acute pancreatitis

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Key words
acute pancreatitis, C-reactive protein, interleukin-10, interleukin-6, inflammatory markers, interleukins, percutaneous catheter drainage.

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Abstract

Background: Percutaneous catheter drainage (PCD) is used as the first step in the management of symptomatic fluid collections in patients with acute pancreatitis (AP). There are limited data on the effect of PCD on inflammatory markers.
Aim: To study the effects of PCD on serum levels of C-reactive protein (CRP), IL-6, and IL-10 and its correlation with the outcome.
Methods: Consecutive patients of AP with symptomatic fluid collections undergoing PCD were evaluated for serum levels of CRP, IL-6, and IL-10 before PCD and at 3 and 7 days after PCD. Resolution of organ failure (OF), sepsis, and pressure symptoms was considered to demonstrate the success of PCD. Changes in levels following PCD were correlated with outcome.
Results: Indications of PCD in 59 patients (age 38.9 ± 13.17 years, 49 male) were suspected/documented infected pancreatic necrosis (n = 45), persistent OF (n = 40), and pressure symptoms (n = 7). A total of 49 (83.1%) patients improved with PCD, five patients required surgery, and six died. A significant difference was noted between baseline levels of CRP (P = 0.026) and IL-6 (P = 0.013) among patients who improved compared to those who worsened following PCD. Significant decrease (P < 0.01) of all three markers on day 3 of PCD insertion, with further decrease (P < 0.01) on day 7, was noted. The percentage of the decrease of IL-6 levels on day 3 and of CRP on day 7 correlated with the outcome.
Conclusion: PCD is associated with a significant decrease in CRP, IL-6, and IL-10 levels. Percentage decrease in IL-6 on day 3 and CRP on day 7 correlated with the outcome of patients managed with PCD.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas with involvement of both local tissues and distant organs. During an episode of AP, large quantities of cytokines, such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-8 (IL-8), are produced, which have a key role in the pathogenesis of AP.[1–3] Cytokines stimulate transcription factor NF-κB, which plays a pivotal role in the expression of numerous genes involved in inflammation.[4] This cytokine storm is followed by an anti-inflammatory response, and the severity depends on the balance between inflammatory and anti-inflammatory response.[5] The evolution of AP occurs in two phases: an early phase (usually within the first week of onset) and a subsequent phase occurring after the first week of the onset of the disease.[6] During the first phase, the severity of pancreatitis is related to the systemic inflammatory response elicited by the tissue injury, and in the second phase, the severity of disease and mortality is usually related to the infection of pancreatic necrosis.[6]

The revised Atlanta classification[6] of severity of AP is based on the presence/absence of organ failure (OF) and/or fluid collections. Percutaneous catheter drainage (PCD) of symptomatic fluid collections in patients with AP is a minimally invasive alternative to surgical treatment and has lead to a paradigm shift in the management of pancreatic fluid collections from open necrosectomy to minimally invasive treatment. Most of the centers have now adopted the "step up" approach based on the PANTER trial,[7] the first step being percutaneous or endoscopic catheter drainage. A recent meta-analysis showed that the nonoperative approach to percutaneous drainage is successful in up to 50% of patient with infected necrosis.[8] Van Baal *et al.*[9] also reported that, when PCD is used in necrotizing pancreatitis,

surgical necrosectomy could be avoided in over half of the patients. Patients failing to recover with medical management and PCD need a step up approach to treatment in the form of single- or multiport percutaneous endoscopic necrosectomy[10] or video-assisted retroperitoneal debridement (VARD).[7] Patients not responding to these minimally invasive necrosectomy techniques will ultimately require surgical necrosectomy, with higher mortality up to 40%.[11]

While the usefulness of serum levels of IL-6,[12,13] IL-10,[14] and C-reactive protein (CRP)[15–18] in the assessment of the severity of AP and mortality have been studied, they have not been evaluated for assessing the outcome of PCD. A few studies have documented that the levels of CRP fall after PCD.[19–23] One study showed that there was a correlation between the decrease in CRP levels and outcome of patients after PCD.[23] There are no such data on IL-6 and IL-10. Hence, we planned the current study to observe the effect of PCD on serum levels of CRP, IL-6, and IL-10 and whether the change in levels after PCD could correlate with the outcome of the patients.

Patients and methods

This study comprised of all patients of AP having fluid collection(s) admitted to the Gastroenterology and Surgery services at the Postgraduate Institute of Medical Education and Research, a tertiary care referral center in Chandigarh, India, who underwent PCD as a part of treatment between July 2015 and December 2016. This prospective observational study was approved by the Institute Ethics Committee, and informed consent was obtained from all the patients before inclusion.

Patients. A total of 105 patients with AP aged > 12 years having fluid collection(s) were admitted in the hospital, 59 of whom underwent PCD and formed the study group. Patient with underlying chronic pancreatitis or those having undergone any prior endoscopic/ radiological/ surgical intervention or PCD outside the study center were excluded from the study. Patients with known severe pre-existing comorbid illnesses were also excluded.

Treatment protocol. The diagnosis of AP was made by any two of the following three factors: (i) abdominal pain consistent with AP; (ii) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (iii) characteristic findings of AP on contrast-enhanced computed tomography (CECT) and less commonly on magnetic resonance imaging (MRI) or transabdominal ultrasonography.[6] Severe AP was defined by the presence of persistent OF and moderately severe pancreatitis defined as local/systemic complications without persistent OF based on modified Marshall scoring system.[24] A score of ≥2 in the modified Marshall scoring system for organ dysfunction was defined as the presence of OF, transient if OF resolved within 48 h, and persistent beyond 48 h.[24] Infected necrosis was diagnosed in the presence of a positive culture in the initial aspirate from the pancreatic collection, presence of air on computed tomography or microbial growth in blood culture, and improvement with PCD. All patients were managed according to standard recommendations, which included intensive resuscitation, fluid and electrolyte monitoring, nutritional support, and supportive care.[25] Antibiotics were not used for pancreatic collections unless infection was strongly suspected, even with severe AP. All the patients were subjected to CECT abdomen before PCD, unless the patient was clinically unstable to be shifted or in the presence of renal failure.

Percutaneous catheter drainage

Procedure. The indications for PCD were persistent OF, suspected infected necrosis, and/or pressure symptoms such as pain or gastric outlet obstruction. The site, route, and image guidance (CT/USG) of PCD were chosen by the interventional radiologist based on the location, size, and extent of the pancreatic collections. Preprocedure optimization of coagulation parameters was performed. Intra-abdominal pressure (IAP) was measured 6–12 h before PCD insertion using the Foley manometer technique.[26] The technique used for PCD was either Tandem trocar or Seldinger technique depending on the size and site of collection(s),[27] and an initial catheter size of 12 Fr was used for PCD. The first aspirated fluid sample was transferred to the bacteriology laboratory in a sterile container for culture. The catheter was left for gravity drainage and flushed with normal saline at least once a day.

Post-PCD follow-up. Postprocedure, patients were monitored for improvement in OF, control of infection, and relief of pressure symptoms, and IAP was measured at 24 and 48 h post-PCD. In the event of no improvement within 72 h, the catheters were upsized to a maximum of 16 Fr, or additional drainage was established for any residual collection(s). After the drainage procedure, antibiotic therapy was modified according to the culture sensitivity report and was continued for at least 10–14 days. All patients were followed up clinically and radiologically (USG/CECT) until discharge, and thereafter, imaging was repeated at 2–4 weeks until resolution or surgery/death. Patients who failed to recover or worsened with medical management and PCD underwent surgical necrosectomy.

All immediate periprocedural, as well as delayed, complications of PCD were noted. External pancreatic fistula (EPF) with clear pancreatic secretion of ≥100 mL per day persisting beyond 2 weeks of insertion of PCD were managed using pancreatic duct stenting. Patients with slippage and blockade of catheter were readmitted and managed with reintroduction of PCD. Bleeding from the PCD site was investigated and managed as per the indication.

Inflammatory markers. Blood samples were collected for CRP, IL-6, and IL-10 on the day of PCD and 3 days and 7 days after PCD. Quantitative CRP estimation was performed by using latex-enhanced nephelometry. Samples for IL-6 and IL-10 were centrifuged and stored at −80°C for subsequent batch analysis. IL-6 and IL-10 estimation was performed using commercially available ELISA kits (Diaclone ELISA kit, Diaclone SAS, France).

Statistical analysis. All data were entered on a personal computer using Microsoft Excel 2010 and SPSS software. The data were analyzed using SPSS software (version 22.0, IBM, USA). Quantitative or numerical variables were represented with measures of central location, such as mean; median; and measures of dispersion, that is, standard deviation, standard error.

The correlation between inflammatory marker levels before PCD and the duration of OF, duration of PCD, and hospital stay was calculated by the Pearson correlation test (r) while the correlation with the requirement of additional PCD, requirement of upgradation of PCD, requirement surgery, and mortality was calculated by the Spearman rank test (rho). For more than two groups, one-way ANOVA was used. A P value of less than 0.05 was statistically significant.

Results

Of the 59 patients, 23 (39%) required intensive care, with 8 patients requiring ventilator support and 4 patients requiring dialysis. Table 1 demonstrates the patient characteristics. The indications of PCD were suspected/documented infected necrosis in 45 patients, persistent OF in 40 patients, and pressure symptoms in 7 patients. One PCD was inserted in 32 (54.2%) patients, whereas 27 (45.8%) patients had ≥2 PCDs with mean of 1.64 ± 0.78 PCDs per patient. The first PCD was upgraded in 27 (45.8%) patients. Overall, 49 of 59 (83.1%) patients improved after PCD, with the resolution of fluid collections, OF, sepsis, and/or pressure symptoms (Fig. 1). Five patients required open necrosectomy for failure to respond with PCD, and six (10.2%) patients died, including one patient after surgery (Fig. 2). The mean hospital stay was 30.6 ± 17.11 days.

All our study patients were discharged with PCD in situ. A total of 37 complications occurred in 33 of 55(60%) patients, EPF being the most common (n = 19), followed by slippage of PCD catheter (n = 10) and blockade of PCD catheter (n = 7), and one patient developed a bleed through the PCD catheter. Ten of the patients with EPF were managed conservatively, and the fistula output decreased gradually until it stopped. The other nine patients underwent successful endoscopic pancreatic stenting with resolution of fistula. Patients with slippage or block of PCD were readmitted, and repositioning of PCD was performed. One patient who developed bleeding from the cavity wall was successfully managed with surgical packing. The median duration of PCD1 was 19 (range; 5–94) days, PCD2 was 26 (range; 4–96) days, and PCD3 was 30.5 (range; 5–90) days.

Table 1 Patient characteristics (n = 59)

Age (mean ± SD)	38.9 ± 13.17 years
Gender (M:F)	49:10
Etiology of pancreatitis	
Alcohol	36 (61%)
Gall stone	12 (20.3%)
Others	11 (18.7)
Organ failure	
Acute lung injury	42 (71.2%)
Acute kidney injury	14 (23.7%)
Cardiovascular system failure	6 (10.2%)
Infection of pancreatic collection	
Infected	38 (64.4%)
Sterile	21 (35.6%)
CT severity index (CTSI) (mean ± SD)	9.49 ± 1.04
Interval between pain onset to hospitalization (median/range)	13 days (1–90 days)
Interval between pain onset to first PCD (mean ± SD)	23.76 ± 17.43 days

PCD, percutaneous catheter drainage.

Levels of inflammatory markers. The mean values of CRP before the placement of PCD were 153.71 ± 105.10 mg/L, of IL-6174.52 ± 54.32 pg./mL, and that of IL-10 were 31.91 ± 15.62 pg./mL. Of the 59 patients, 43 (72.9%) had acute necrotic collection (ANC), and 16 (27.1%) had walled-off necrosis (WON). The mean baseline values of CRP in ANC and WON were 148.86 ± 93.76 mg/L and 166.75 ± 133.59 mg/L, respectively (P = 0.56). The mean baseline values of IL-6 in ANC and WON were 184.51 ± 53.07 pg./ml and 142.76 ± 47.75 pg./ml, respectively (P = 0.007). The mean baseline values of IL-10 in ANC and WON were 35.38 ± 16.29 pg./ml and 22.57 ± 8.55 pg./ml, respectively (P = 0.004).

Table 2 demonstrates the correlation between baseline levels of inflammatory markers and outcome measures. Serum CRP levels correlated positively with the duration of OF and mortality, whereas serum IL-6 levels correlated with mortality.

Effect of PCD on inflammatory markers. Figure 3 depicts the levels of inflammatory markers before PCD and 3 days and 7 days after insertion of PCD. There was a significant decrease in all the three markers on day 3 after the PCD was inserted, with further decrease on day 7 as well. Table 3 compares the baseline levels of inflammatory markers among 49 patients who improved and 10 patients who did not. Levels of all the three markers were higher among the patients who worsened or required surgery. Baseline CRP and IL-6 levels were significantly higher in patients who did not improve or worsened after PCD compared to those who improved ($P < 0.05$).

Table 4 gives the correlation between the decrease of inflammatory markers on days 3 and 7 post-PCD and improvement after PCD. The correlation of the decrease of the three markers with improvement after PCD did not reach statistical significance. When the percentage of the decrease of inflammatory markers on days 3 and 7 after PCD insertion was compared between patients who improved (n = 49) and those who worsened or required surgery or died (n = 10), the decrease of IL-6 levels on day 3 and that of CRP levels on day 7 correlated positively with the outcome of patients ($P < 0.05$).

Discussion

We evaluated serum CRP, IL-6, and IL-10 levels in 59 patients with symptomatic pancreatic fluid collections before PCD and 3 and 7 days after PCD. There was a significant difference between baseline levels of CRP and IL-6 among patients who improved after PCD (n = 49) compared to those who worsened (n = 10) but not in the levels of IL-10. There was a significant decline in the levels of all three markers after 3 and 7 days of PCD, and the percentage decrease of CRP on day 7 post-PCD and that of IL-6 on day 3 post-PCD correlated with the outcome.

Serum CRP levels have been found to correlate with the severity of AP and outcome.[15–18,28] Serum CRP values reach a peak on day 3 of pancreatitis and decline after that.[13] Patients with severe AP with a high Acute Physiology and Chronic Health Evaluation (APACHE) score can have persistently elevated levels beyond 7 days.[5] It is expected that if there is

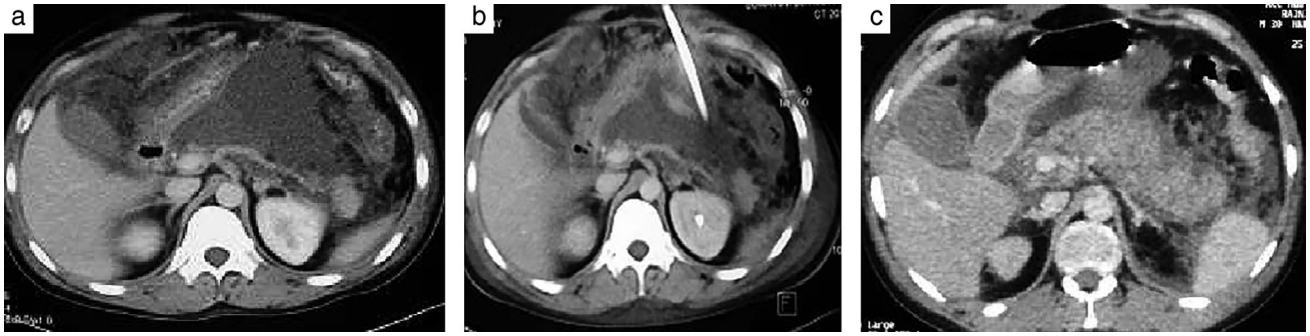

Figure 1 Contrast-enhanced computed tomography (CECT) abdomen; (a) before percutaneous catheter drainage (PCD), (b) with PCD, (c) after PCD.

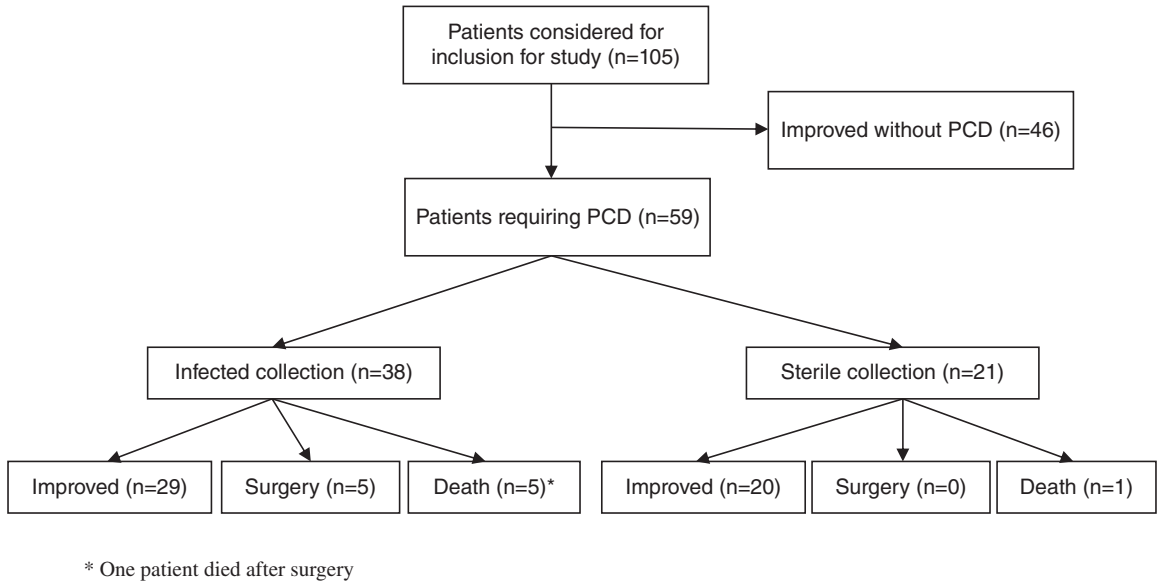

Figure 2 Scheme of treatment in patients and outcome.

Table 2 Correlation of inflammatory markers with outcome

	Serum CRP		Serum IL-6		Serum IL-10	
Outcome parameters	Correlation	Significance (*P*)	Correlation	Significance (*P*)	Correlation	Significance (*P*)
Duration of organ failure (*r*)	0.33	0.01	0.06	0.72	0.07	0.68
Duration of PCD (*r*)	0.03	0.80	0.01	0.78	−0.14	0.28
Requirement of additional PCD (rho)	0.19	0.14	0.05	0.67	0.14	0.27
Requirement of upgradation of PCD (rho)	0.13	0.32	0.03	0.77	−0.08	0.52
Hospital stay (*r*)	0.02	0.87	0.20	0.12	0.09	0.48
Requirement of surgery (rho)	0.11	0.37	0.05	0.72	−0.01	0.97
Mortality (rho)	0.26	0.04	0.33	0.01	0.17	0.18

CRP, C-reactive protein; PCD, percutaneous catheter drainage.

persistence of inflammation in patients with infected necrosis, the serum CRP level would tend to remain elevated. Navalho *et al.*[23] reported that their patients with infected fluid collections had CRP levels in the range of 172.8–190.9 mg/l at the time of PCD. We also found that our patients with fluid collections requiring PCD had elevated CRP levels more than 3 weeks after the onset of pancreatitis, and the levels correlated with the persistence of OF and subsequent mortality. We have, for the first time, noted that baseline serum CRP levels were higher among patients who did not improve after PCD. There are a few studies on changes in CRP

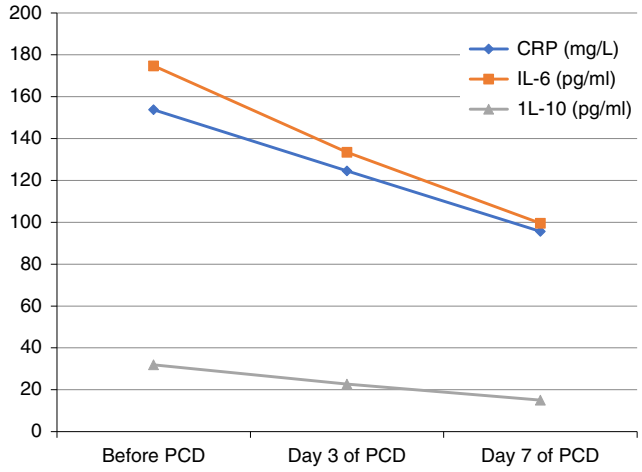

Figure 3 Levels of inflammatory markers before and days 3 and 7 post-PCD. PCD, percutaneous catheter drainage.

Table 3 Comparison between patients who improved and those who did not with PCD

Parameters	Patients who improved	Patient who did not improve	Significance (*P*)
CRP (mg/L)	146.48 ± 111.60	189.10 ± 55.5	0.026
IL-6 (pg/ml)	166.09 ± 51.21	215.81 ± 52.40	0.013
IL-10 (pg/mL)	30.28 ± 14.13	39.90 ± 20.53	0.076

CRP, C-reactive protein; PCD, percutaneous catheter drainage.

levels in patients undergoing PCD. Baudin *et al.*[19] and Kotan *et al.*[20] were the first to show that CRP levels decrease following PCD. Navalho *et al.*[23] showed that, after PCD, the serum CRP levels fell significantly and correlated with the success of the procedure. Ai *et al.*[21] compared the decrease in CRP levels after PCD and surgical necrosectomy and documented that CRP levels return to normal 24.9 days after PCD and 42.1 days after surgery. We estimated CRP levels on days 3 and 7 after PCD and found that the fall of levels correlated with the outcome of PCD.

Among the cytokines studied in patients with AP, levels of both IL-6 and IL-10 are elevated in AP and correlate with severity, OF, and mortality.[29–31] Brivet *et al.*[32] observed that levels of both IL-6 and IL-10 remain elevated in systemic circulation for up to 15 days in severe pancreatitis. The persistence of inflammation or OF or the occurrence of infection has also been found to be associated with persistently elevated IL-6 and IL-10 levels.[33]

We observed higher levels of both IL-6 and IL-10 in our patients with pancreatic collections more than 3 weeks after the onset of pain. When we correlated baseline IL-6 and IL-10 levels with outcome measures, there was a positive correlation between mortality and IL-6 levels but not with IL-10 levels. After the institution of PCD, there was a significant decrease in IL-6 and IL-10 levels on day 3, which fell further on day 7 after PCD. There is only one previous study that had looked at IL-6 and IL-10 levels after PCD in which Liu *et al.*[22] reported a decrease in IL-6 and IL-10 after PCD. They have compared the effect of

Table 4 Correlation of fall of inflammatory markers with outcome

Parameters	Outcome	Before PCD	Day 3	Day 7	% of fall on day 3	% of fall on day 7	p1	p2	p3	p4
CRP (mg/L)	Improved	146.48 ± 111.60	113.7 ± 75.58	81.72 ± 61.28	11.37 ± 37.86	34.38 ± 36.03	0.31	0.10	0.80	0.04
	Not improved	189.1 ± 55.5	173.6 ± 69.04	161.8 ± 81.9	8.25 ± 22.40	13.99 ± 31.81				
IL-6 (pg/mL)	Improved	163.79 ± 51.21	121.3 ± 38.87	85.18 ± 28.58	24.65 ± 13.86	45.20 ± 18.80	0.28	0.78	0.04	0.13
	Not improved	215.81 ± 52.40	184.3 ± 55.7	128.0 ± 63.57	15.04 ± 11.29	34.61 ± 25.43				
IL-10 (pg/mL)	Improved	29.95 ± 14.13	20.56 ± 9.25	13.25 ± 5.66	29.33 ± 15.24	52.22 ± 15.38	0.65	0.97	0.27	0.07
	Not improved	39.9 ± 20.53	31.84 ± 21.25	23.24 ± 16.16	23.21 ± 19.32	42.10 ± 20.44				

p1, significance of fall on day 3; p2, significance of fall on day 7; p3, significance of percentage of fall on day 3; p4, significance of percentage of fall on day 7.
CRP, C-reactive protein; PCD, percutaneous catheter drainage.

PCD alone with PCD plus abdominal fluid drainage on levels of IL-6 and IL-10. In a different setting, Bakker *et al.*[34] studied the impact of endoscopic and surgical necrosectomy on serum IL-6 levels and observed a significant decrease in IL-6 levels. These results suggest that both PCD and endoscopic necrosectomy result in a decrease in the levels of inflammatory cytokines.

Our data are in accordance with that of Liu *et al.*,[22] that PCD results in a decrease of inflammatory markers denoting a reduction of inflammatory cytokine drive. In our patients, this happened in all the patients subjected to PCD, with a greater decrease in the patients who improved after PCD. Removal of pancreatic necrosis and/or infected tissue leads to the interruption of the inflammatory cascade and a decrease in IAP resulting in the decrease of serum inflammatory markers.[35] The fact that IL-6 levels fell at day 3 post-PCD and CRP levels at day 7 post-PCD in our study suggests that a halt in macrophage stimulation by IL-6 is followed by a decrease in CRP production. While we estimated levels of CRP, IL-6, and IL-10 only on days 3 and 7 of PCD, other workers have estimated levels of CRP periodically until the removal of the PCD catheter.[19,23] It has been noted that the levels of inflammatory markers did not return to normal even at the time of removal of the PCD catheter in these studies.[19,22,23] Our result showed that, although the decrease in absolute values of the three markers did not correlate with the outcome, the percentage fall in levels on days 3 and 7 correlated with the outcome. By extending the estimation beyond 7 days, till discharge or till removal of catheter, we might have obtained a better statistical correlation of fall in levels, but a 3-day and 7-day estimation is a more practical and feasible approach.

Our results suggest that monitoring the levels of CRP, IL-6, and IL-10 after PCD can be used to predict the outcome of PCD. Patients who do not show a decrease of CRP and IL-6 are candidates who may require a stepping up of the treatment strategy with endoscopic or surgical necrosectomy. However, our study suffers from some limitations. We did not have levels of the three markers on the day of hospitalization. As such, our hospital being a tertiary care hospital, the mean interval between onset of pain and hospitalization was 13 days. We did not have a control group of patients with fluid collections who did not require PCD. We estimated levels of CRP, IL-6, and IL-10 on days 3 and 7 post-PCD only. We did not estimate the levels until the day of discharge or until removal of PCD. Our premise was to see if a trend in the change of levels of the inflammatory markers could predict the outcome.

In conclusion, percutaneous drainage of peripancreatic fluid collections is rewarding in a majority of patients. Serum levels of CRP and IL-6 before placement of PCD correlated with the outcome of patients managed with PCD. PCD leads to a significant fall in inflammatory markers, which can be used to correlate with the outcome. We propose that the monitoring of levels of CRP and IL-6 should be performed after PCD to identify poor responders who may require stepping up of the treatment strategy.

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