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Original Article

Timing of surgical intervention in patients of infected necrotizing pancreatitis not responding to percutaneous catheter drainage

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ABSTRACT

Background: The timing of surgery in patients not responding to percutaneous catheter drainage (PCD) in infected pancreatic necrosis remains challenging.
Materials and methods: A randomized controlled trial was designed to establish the optimal timings of surgery following PCD in patients with infected pancreatic necrosis (IPN). Patients who did not improve by day 10 after PCD insertion were included in the present study and were randomized to group A (**step-up approach as a bridge to surgery**) or group B (**step-up approach with intention to avoid surgery**). Weekly inflammatory and nutritional markers were monitored in both groups (clinical trials. gov identifier NCT-01527084).
Results: From July 2011 to December 2012, 40 patients underwent treatment with PCD. The first 8 patients were randomized into two groups. The trial was stopped prematurely because of difficulty in accrual and poor progress. All subsequent patients were managed with step-up approach with the intention to avoid surgery. Of 35 patients, 24 patients were managed by PCD alone while 11 patients required surgery. In patients who did not require surgery; levels of serum high sensitivity C-reactive protein (hsCRP), interleukin-6(IL6) and prealbumin showed a falling trend. This group also had higher baseline albumin and higher albumin at 4 weeks.
Conclusion: During the present study, randomization into surgery at a predetermined time in step-up approach was discontinued due to poor progress. Step-up approach with the intention to avoid surgery led to a success rate of 68.5%. The present study failed to predict the optimal timing of surgery after PCD. Patients who needed surgery were sicker at the time of admission, had higher incidence of organ failure, and spent more time in the ICU compared to patients who did not need surgery. In future, inflammatory and nutritional markers may be useful to identify patients who are unlikely to respond to PCD and may help determine the timing of surgery.

1. Introduction

In the scientific literature, there are no reports on the timing of surgery in patients not responding to percutaneous catheter drainage (PCD). Recently published IAP/APA evidence-based guidelines for the management of acute pancreatitis recommended that the timing of repeat interventions (e.g. repeat percutaneous drainage, repeat endoscopic necrosectomy, or crossover to surgery) should be based on clinical and imaging criteria [1].

The "Step-up approach" is rapidly being adopted as the standard of care in infected pancreatic necrosis (IPN). However, two methods are currently emerging depending on use of different timings for

Abbreviations: PCD, Percutaneous catheter drainage; IPN, Infected pancreatic necrosis; VARD, Videoscopic assisted retroperitoneal debridement; hsCRP, High sensitivity C-reactive protein; IL-6, Interleukin 6; MDA, Malondialdehyde.

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surgical intervention: a **"Step-up approach as a bridge to surgery"** and a **"Step-up approach with intention of avoiding surgery"**. In the PANTER trial 'Step-up approach' was used as a "bridge to surgery" which consisted of PCD as a first step followed by videoscopic assisted retroperitoneal debridement (VARD), if necessary. In that study, more than a third of patients with infected necrotizing pancreatitis did not require surgery and were successfully managed with PCD alone.[2]In our previous study of 56 patients managed initially with PCD, surgery could be avoided in 48% of patients, with reversal of organ failure in 62% of patients [3]. We used step-up approach with "intention of avoiding surgery" with extended use of PCD. This study involved aggressive use of percutaneous catheters along with large-volume saline irrigation, which helped in the evacuation of the infected fluid, debris, necrotic tissue from the cavities; while surgery was performed on demand [3].

We designed the present study to address the issue of timing of surgical intervention after step-up approach in patients managed initially by PCD catheter and saline irrigation. These patients were randomized into two groups. In one group, surgical intervention was planned at 10–15 days after PCD insertion where step up approach was used as a "bridge to surgery". In the other group step up approach was used with the" intention to avoid necrosectomy" and to offer surgery only on demand.

In the present study levels of inflammatory and nutritional markers were measured weekly in both groups. The usefulness of these markers in deciding the timing of surgery has not been previously studied.

2. Materials and methods

In this prospective study, all patients of Infected Pancreatic Necrosis (IPN) managed with PCD and saline irrigation in the Division of Surgical Gastroenterology, and the Department of Gastroenterology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh from July 2011 to December 2012 were included. The diagnosis of IPN was based on clinical findings, biochemical and microbiological parameters, and CT severity index (UK GUIDELINES) [4]. All patients provided written informed consent before enrollment. This study was conducted according to the guidelines set up by the Helsinki Declaration (modified 2000). The institutional ethics committee approved the protocol. The study is registered with clinical trials.gov with the identifier NCT-01527084.

2.1. Inclusion criteria

All patients with the diagnosis of IPN (UK GUIDELINES [4]) managed with PCD for 10–15 days and those who did not show significant improvement on PCD.

2.2. Exclusion criteria

1. Patients who showed significant improvement on PCD within 10 days of its insertion. (Criteria for significant improvement on PCD included one or more of the following: defervescence, acceptance of enteral nutrition, decrease in total leukocyte count, reversal of organ system failure [3]).
2. Sterile pancreatic necrosis.
3. An acute intra-abdominal event (perforation of hollow viscus, bleeding, or abdominal compartment syndrome) during or within 10 days, after PCD insertion.
4. Previous drainage or surgical necrosectomy for infected pancreatic necrosis (ERCP, with or without papillotomy was allowed).
5. Previous exploratory laparotomy for acute abdomen and diagnosis of pancreatitis during laparotomy.

2.3. Treatment protocol

All patients with severe acute pancreatitis (Revised Atlanta criteria [5]) underwent blood investigations, which included complete haemogram, coagulogram, serum calcium levels, renal and liver function tests and blood gas analysis within 48 h of admission. In presence of fever, blood cultures for bacterial and fungal growth were taken. All the patients referred to the unit were on antibiotics at the time of referral. Subsequently antibiotics were changed according to culture sensitivity. A modified Marshall's score (for organ failure), APACHE II score and modified CTSI score were calculated for each patient at the time of admission and also serially calculated both before and after intervention. All patients were fed orally or through a naso-jejunal tube after initial medical management and fluid resuscitation. Parenteral nutrition (PN) was instituted if the enteral route was not available due to persistent ileus or if the daily requirement of the patient was not being meet by enteral feeding alone.

2.4. Inflammatory markers and nutritional markers

Serial measurement of inflammatory markers (C-reactive protein, IL-6 and Malondialdehyde) and nutritional markers (Albumin and pre_albumin) were done once a week every week. Serum high sensitivity C- reactive protein (hsCRP) levels were estimated using an ELISA based kit, as per the manufacturer's protocol (Diagnostic Biochem Canada Inc, Canada). Serum Interleukin 6 (IL_6) levels were also estimated using an ELISA based kit as per the manufacturer's protocol (Diaclone, France). Malondialdehyde (MDA) was estimated using Stocks and Dormandy method [6]. Serum albumin was estimated using a Hitachi module P800 automated clinical chemistry analyzer (Roche Diagnostics, Germany). Serum prealbumin levels were estimated using an ELISA based kit as per the manufacturer's protocol (Assaypro, St. Charles).

2.5. Step-up approach [2,3].

All patients underwent step up approach as described in our previous study [3]. Patients who had been on PCDs for 10 days without improvement and had been referred to us for surgery were recruited in the present study. These patients were then randomized to group A (**Step-up approach as a bridge to surgery**) or group B (**Step-up approach with intention to avoid surgery**). The surgical procedures for both groups were open necrosectomy and closed lesser sac drainage or retroperitoneal necrosectomy. Feeding jejunostomy was performed routinely unless it was not possible due to dense bowel adhesions. Accordingly, patients in group A underwent surgery between day 10–15 after PCD while patients in group B were continued with PCD and saline irrigation beyond 15 days. The following criteria were used to determine whether surgery was necessary in patients in group B:

1 Persistent sepsis or symptoms
2 Worsening of clinical condition
3 Failure to thrive
4 Complications of SAP or PCD

All patients were clinically assessed twice a day and the decision for surgery was made by the senior attending (RG).

Assessment was based on the following primary and secondary end points:

2.6. Primary end points

1. Mortality or complete recovery in two groups

2. Morbidity in two groups
3. Proportion of patients in whom surgery would be avoided in Group B

2.7. Secondary end points

1. Reversal of existing organ failure
2. New onset multiorgan failure or sepsis and systemic complications
3. Total number of PCD catheters used, and catheter/drain related complications, and any intervention required.
4. Locoregional complications such as pseudocyst, Pancreatic fistula, Enteric fistula
5. Perforation of a hollow viscus and bleeding requiring intervention

2.8. Statistical analysis

Randomization was performed using a computer-generated table of random numbers at a block of four patients. Allotment into two groups was done using serially-numbered envelopes. Continuous data were given as mean ± standard deviation (SD) or median and interquartile range, as appropriate. The normality of quantitative data was checked using Kolmogorov Smirnov tests. The Mann-Whitney *U* test was used for statistical analysis of skewed continuous variables for two groups. For normally distributed data a *t*-test was applied. For more than two visits data, One −Way ANOVA followed by Post Hoc multiple comparisons was applied. Discrete categorical data were presented as *n* (%). Categorical data comparisons were made using a Pearson Chi-square test and Fisher's exact test, as appropriate. To estimate independent predictors for PCD outcome, logistic regression analysis was applied. All analyses were conducted using computer program SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and performed at a significance level of $\alpha = 0.05$.

3. Results

We randomized the first 8 patients into two groups using a table of random numbers at block of 4 patients following a **"Step-up approach as a bridge to surgery"** and **"Step-up approach with intention to avoid surgery"**. However, randomization was discontinued at 6 months due to the poor progress of the study. Reasons for the poor progress of randomized controlled study were: (1) Patients in group A withdrew consent for necrosectomy after initial recruitment to avoid surgery; (2) Patients continued to be hemodynamically unstable even after PCD insertion and were therefore unsuitable candidates for randomization into group A; (3) The length of time required to complete the first two block of patients as per table of random numbers took 6 months. No meaningful conclusion could be derived from the study, despite a higher mortality rate in group A, i.e., 3 of 4 patients, compared to a mortality rate of 1 of 4 patients in group B. After randomization was discontinued, all subsequent patients recruited for the study (32) underwent **Step-up approach with intention to avoid surgery**. Twenty five of 36 patients, including 4 patients in the randomized part of the study, were successfully managed without necrosectomy using a step-up approach with intention to avoid surgery. One patient who was showing improvement opted for early surgery and was excluded from final analysis. Only 11 patients needed necrosectomy. Depending on the need of surgery, patients were distributed into two groups, patients for whom surgery could be avoided and patients who needed surgery. The two groups were compared subsequently.

3.1. Patient characteristics

Demographic data between patients who needed surgery and in whom surgery could be avoided were comparable. A higher number of patients with alcoholic pancreatitis needed surgery (p-0.017) (Table 1).

3.2. Clinical and laboratory parameters

The incidence of hypocalcaemia at admission was significantly higher in patients who needed surgery (p-0.03). Twenty-two patients (61.1%) in the combined group had an APACHE II score of >8, out of which 20 patients (55.5%) had APACHE II score of >8 at admission while another two patients at time of PCD insertion. Patients who avoided surgery had a lower mean APACHE II score at admission and before PCD insertion than patients who needed surgery. It should be noted however, that only the difference in the APACHE II score at admission had statistical significance (7.6 ± 2.5 vs 10.5 ± 4.2, p-0.036 and 8.2 ± 3.3 vs. 10.4 ± 3.9, $p = 0.078$ respectively). All the patients who underwent surgery had significantly longer preoperative ICU stay (p-0.003) and had extrapancreatic necrosis. There was no statistically significant difference in between the groups with respect to the extent of necrosis during the hospital stay, the site of intrapancreatic necrosis, the incidence of complete pancreatic necrosis and emphysematous necrosis (Table 2). With respect to sites of extrapancreatic necrosis, patients who required a necrosectomy had significantly increased incidence of extrapancreatic necrosis in the left anterior and posterior pararenal spaces ($p = 0.010$ and 0.015 respectively).

3.3. Organ failure (Table 3)

A modified Marshall's score was used for organ failure assessment. Organ failure (single or multiple) was present in 31 of 36 patients (86.1%) in the present study. Persistent organ failure was present in 30(83.3%), while transient organ failure was noted in 1 patient. All patients who needed necrosectomy had single or multiorgan failure (p-0.001). The mean number of organs that failed in the two groups was also significantly different (1.5 ± 0.7 v/s 0.8 ± 0.4, $p = 0.009$). However, the duration of organ failure including incidence of respiratory failure was comparable in both groups (Table 3). Of the 8 patients who needed ventilatory support after respiratory failure, seven patients required surgery after PCD. The incidence of renal and cardiovascular failure was higher in patients who needed surgery; though only the difference in the incidence of cardiovascular failure reached statistical significance (36.4% versus 8.3%,p-0.23 and 45.4% versus 4.2% $p = 0.007$ respectively).

A total of 8 patients developed late-onset organ failure. Three of 8 patients developed late onset cardiovascular failure, two patients experienced respiratory failure and three developed both respiratory and cardiovascular failure. Six out of 8 patients were in the group who needed surgery and the difference was statistically significant compared to the group of patients in whom surgery was avoided (p-0.002).

3.4. Microbiological data (Table 4)

Fourteen of 36 patients (38.8%) patients had positive blood culture before and after PCD. Eight organisms were isolated with E. Coli, α-hemolytic streptococci and coagulase negative staphylococcus aureus being most common. There was no statistically

Table 1
Details and comparison of patient characteristics, investigations and severity.

	Total (n = 36[a])	Non surgical group (n = 24)	Surgical group (n = 11)	p value
Mean Age (Years, Mean ± SD)	39.9 ± 13.6	41.7 ± 13.8	37.3 ± 13	0.409
Male: Female	1.1:1	1:1.4	1:2.6	0.146
Etiology				
Gallstone	17(47.2)	16(66.7)	1(9.1)	0.017
Alcohol Abuse	14(38.9)	6(25)	7(63.6)	
Gallstones & alcohol abuse	2(5.6)	1(4.2)	1(9.1)	
Others	3(8.3)	1(4.2)	2(18.2)	
Referral after onset of symptoms (Days, Mean ± SD)	23.3 ± 31.2	26.2 ± 37.2	18 ± 12.8	0.943
Mean hospital stay(Days, Mean ± SD)	45.58 ± 23.1	43.4 ± 21.3	50.2 ± 27.8	0.494
Mean preoperative ICU stay(Days, Mean ± SD)	7.3 ± 10.2	3.42 ± 5.7	15 ± 13.4	0.003
Patients with hypocalcemia at admission (%)	20 (55.6)	10 (41.7)	9 (81.8)	0.030
Mean Initial APCHE II score	8.3 ± 3.4	7.5 ± 2.5	10.5 ± 4.2	0.036
Mean APACHE II score at first PCD	8.9 ± 3.5	8.2 ± 3.2	10.3 ± 3.9	0.078
Mean modified CTSI Score at admission	8.33 ± 1.88	8.4 ± 1.9	8.1 ± 1.8	0.713
Presence of intra-pancreatic necrosis (%)	27(75)	18(75)	8(72.2)	1
Max. extent of necrosis during stay (%)				
<30%	6(16.7)	2(8.3)	3(27.3)	0.351
30–50%	5(13.9)	3(12.5)	2(18.2)	
>50%	16(44.4)	13(54.2)	3(27.3)	

[a] One patient who was improving on PCD alone opted for surgery and thus excluded from final analysis.

Table 2
Details and comparison of pancreatic necrosis on contract enhanced CT abdomen.

	Total (n = 36[a])	Non surgical group (n = 24)	Surgical group (n = 11)	p value
Complete pancreatic necrosis	2(5.6)	1(4.2)	1(9.1)	0.536
Presence of extrapancreatic necrosis	34(94.4)	22(91.7)	11(100)	0.464
Site of intrapancreatic necrosis				
Head + Body + Tail	10(27.8)	8(33.3)	2(18.2)	0.447
Head + Body	5(13.9)	3(12.5)	1(9.1)	1
Body + Tail	8(22.2)	5(20.8)	3(27.3)	0.685
Body only	1(2.8)	1(4.2)	0	1
Tail only	3(8.3)	1(4.2)	2(18.2)	0.469
Site of extrapancreatic necrosis				
Lesser sac	28(77.8)	19(79.2)	8(72.2)	0.492
Gastrohepatic	7(19.4)	6(25)	1(9.1)	0.272
Left perihepatic	2(5.6)	1(4.2)	0	0.686
Mesentry	7(19.4)	3(12.5)	4(36.4)	0.120
Transverse Mesocolon	4(11.1)	2(8.3)	2(18.2)	0.372
Spleen	1(2.8)	1(4.2)	0	0.686
Left anterior PR	18(25)	8(33.3)	9(81.8)	0.010
Left Posterior PR	9(25)	3(12.5)	6(54.5)	0.015
Right Anterior PR	3(8.3)	3(12.5)	0	0.309
Right Posterior PR	2(5.6)	2(8.3)	0	0.464
Bilateral Anterior PR	5(13.9)	3(12.5)	2(18.2)	0.529
Bilateral Posterior PR	1(2.8)	0	1(9.1)	0.314
Left paracolic gutter	2(5.6)	1(4.2)	1(9.1)	0.536
Right paracolic gutter	1(2.8)	1(4.2)	0	0.686
Bilateral paracolic gutter	2(5.6)	1(4.2)	1(9.1)	0.536

[a] One patient who was improving on PCD alone opted for surgery and thus excluded from final analysis.

significant difference in both the groups in terms of incidence of bacteremia and type of organisms isolated. Eight out of 36 patients (22.2%) had positive blood fungal cultures before or after PCD. Candida Tropicalis was the organism most frequently detected in these patients. All of these patients received Amphotericin.

Overall 7 types of bacterial organisms were isolated from pancreatic and/or peripancreatic fluid in our study. Samples were taken at the time of Fine Needle aspiration (FNA) or at time of insertion of PCD and from intraoperative specimen. There was no statistically significant difference in the number and types of organisms isolated between the two groups. Bacterial growth was found in the surgical specimen of all surgical patients, E. coli in four patients and Acinetobacter in three. Furthermore, three of these same patients showed fungal growth in the surgical specimen, with Candida tropicalis in two and Candida glabrata in one patient.

3.5. Inflammatory and nutritional markers

Inflammatory and nutritional markers were measured in 24 patients (18 patients who did not require necrosectomy and 6 patients who underwent a necrosectomy) (Tables 5 and 6). Graphs were plotted to identify a possible trend of inflammatory and nutritional markers over time (Fig. 1).

3.6. Inflammatory markers

Levels of hsCRP (Fig. 1A) and IL-6 (Fig. 1B) showed a rising trend in patients who needed surgery and a falling trend in patients for whom surgery was not required. When we looked at Malondialdehyde (MDA) values, we observed that initial and last median MDA levels were higher in patients who needed surgery (Fig. 1C) (Table 5).

Table 3
Details and comparison of Organ Failure.

	Total (n = 36[a])	Non surgical group (n = 24)	Surgical group (n = 11)	p value
Number of organs failed				
Mean ± SD	1.64 ± 0.798	0.833 ± 0.38	1.5 ± 0.68	0.009
Median(Range)	1(1–3)	1(0–1)	1(1–3)	
Duration of organ failure				
Mean ± SD	9 ± 8.485	5.5 ± 5.1	11 ± 0.323	0.414
Median(Range)	5(1–27)	4(1–15)	7(1–27)	
Organ failure				
No organ failure	6(16.7)	6(25)	0	0.001
Single organ failure	22(61.1)	17(70.8)	5(45.5)	
Multiorgan failure	8(22.2)	1(4.1)	6(54.5)	
New onset organ failure in patient already on PCD	8(22.2)	1(4.2)	6(54.5)	0.002
Respiratory failure	30(83.3)	18(75)	11(100)	0.83
Ventilator support (in days) Mean ± SD	2.36 ± 7.047	0	6.36 ± 11.26	0.002
Pleural drainage/Aspiration	7(19.4)	2(8.3)	4(36.4)	0.63
Renal Failure	6(16.7)	2(8.3)	4(36.4)	0.227
Circulatory failure	7(19.4)	1(4.2)	5(45.4)	0.007

[a] One patient who was improving on PCD alone opted for surgery and thus excluded from final analysis.

Table 4
Details and comparison of microbiological data.

	Total (n = 36[a])	Non surgical group (n = 24)	Surgical group (n = 11)	p value
IPN				
Unimicrobial IPN	17(47.2)	13(54.2)	4(36.3)	
Polymicrobial IPN	19(52.7)	11(45.8)	7(63.7)	0.182
Organisms causing IPN				
E. coli	21(58.3)	15(62.5)	6(54.4)	0.467
Acinatobacter	15(41.7)	7(29.2)	7(63.6)	0.060
Klebsiella	12(33.3)	7(29.2)	4(36.4)	0.479
Pseudomonas	5(13.9)	4(16.7)	1(9.1)	0.491
Staphylococcus	2(15.6)	2(8.3)	0	0.464
Proteus	4(11.1)	1(4.2)	3(27.3)	0.082
Enterococcus	3(8.3)	2(8.3)	1(9.1)	0.691
Positive blood bacterial cultures before or after PCD	14(38.8)	8(33.3)	4(36.3)	0.371
Organism grown inblood culture				
E. coli	3(8.3)	2(8.3)	1(9.1)	0.691
α-hemolytic streptococci	3(8.3)	1(4.2)	1(9.1)	0.536
Coagulase negative staph. aureus	3(8.3)	1(4.2)	2(18.2)	0.227
Staphylococcus	2(5.6)	2(8.3)	0	0.464
Enterococcus fecium	2(5.6)	2(8.3)	0	0.464
Acinatobacter	2(5.6)	1(4.2)	1(9.1)	0.536
Klebsiella	1(2.8)	1(4.2)	0	0.686
Enterobacter	1(2.8)	1(4.2)	0	0.686
Positive Blood fungal culture before or after PCD	8(22.2)	5(20.8)	3(27.3)	0.174
Organisms grown in blood fungal culture				
Candida tropicalis	5(13.9)	3(12.5)	2(18.2)	0.350
Candida albicans	1(2.8)	1(4.2)	0	
Candida glabrata	1(9.1)	0	1(9.1)	
Positive fungal serology before or after PCD	13(36.1)	7(29.2)	5(45.5)	0.463
Fungal infection in drain	4(11.1)	3(12.1)	1(9.1)	0.628

[a] One patient who was improving on PCD alone opted for surgery and thus excluded from final analysis.

3.7. Nutritional markers

Serial levels of serum albumin were measured in both the group. Patients who did not undergo surgery had higher baseline albumin levels showing a rising trend and higher albumin levels at 4 weeks. Surgical patients also showed a rising trend in serum albumin postoperatively, though they had a lower baseline level of albumin and a slower rise in their albumin levels (Table 6) (Fig. 1D). Serum prealbumin levels in patients managed non-surgically showed a continuous decrease; at four weeks, the decrease in their prealbumin level was significant. In patients who needed surgery prealbumin values increased at 4th week. In both groups, the change in level of prealbumin from week 1 to week 4 was statistically significant (p = 0.013 & 0.015 respectively (Fig 1E).

3.8. Characteristics and complications of percutaneous catheter drainage (Table 7)

The total numbers of PCDs used were 84. The diameter of PCDs varied from 10 Fr to 16 Fr. 10 Fr catheter was most commonly used in the study. Catheter diameter used initially was 10 Fr, followed by upsizing to 12 or 14 Fr when required. Large bore catheters (20 Fr–32 Fr) were inserted bedside after marking the site of necrosis/collection under image guidance. Upsizing of PCD catheter was performed in patients with thick outputs clogging the drain and requiring repeated flushing and repositioning. Fifteen patients underwent upsizing of which 6 patients finally needed surgery. The peripancreatic region was the most common site of PCD placement (44.6%), followed by the left pararenal region (36.1%). Patients who needed surgery required a significantly higher number of PCDs in

Table 5
Weekly mean values of inflammatory markers in both the groups.

	Marker	Weeks	Mean	Std. Deviation	p value
Non surgical group (n = 18)	hsCRP (μg/ml)	1	37.11	14.38	0.459
		2	35.72	11.52	
		3	35.81	12.37	
		4	34.94	12.27	
		5	33.41	19.11	
		6	28.10	15.21	
		7	19.66	17.63	
	IL-6(pg/ml)	1	457.35	562.54	0.171
		2	448.44	375.71	
		3	307.72	195.44	
		4	260.72	206.94	
		5	178.42	111.31	
		6	166.00	93.16	
		7	107.66	56.88	
	MDA (mmol/ml)	1	45.36	40.59	0.721
		2	47.96	59.51	
		3	33.66	18.99	
		4	30.20	9.00	
		5	45.35	23.04	
		6	32.80	8.80	
		7	36.71	13.25	
Surgical group (n = 6)	hsCRP (μg/ml)	1	31.83	12.79	0.313
		2	30.33	12.54	
		3	36.50	11.53	
		4	42.00	8.39	
	IL-6(pg/ml)	1	394.33	410.87	0.651
		2	393.00	473.62	
		3	712.33	786.05	
		4	750.83	804.53	
	MDA(mmol/ml)	1	67.66	71.31	0.624
		2	47.87	45.60	
		3	50.26	42.97	
		4	30.96	6.28	

Table 6
Weekly mean values of nutritional markers in both the groups.

	Nutritional marker	Weeks	Mean	Std. Deviation	p value
Non surgical group (n = 18)	Serum albumin(mg/ml)	1	3.30	0.62	0.337
		2	3.17	0.52	
		3	3.23	0.47	
		4	3.41	0.64	
		5	3.60	0.93	
		6	3.72	1.10	
		7	4.00	1.56	
	Serum Prealbumin(μg/ml)	1	95.61	32.07	0.849
		2	91.61	35.96	
		3	90.11	24.14	
		4	87.66	22.89	
		5	83.58	25.2	
		6	100.01	40.33	
		7	112.51	33.62	
Surgical group (n = 6)	Serum albumin(mg/ml)	1	2.76	0.99	0.918
		2	2.95	0.92	
		3	3.00	0.82	
		4	3.13	0.89	
	Serum Prealbumin(μg/ml)	1	82.31	20.25	0.135
		2	90.37	18.81	
		3	85.32	20.90	
		4	159.30	105.08	

left pararenal and right sub-hepatic space (p-0.03 and 0.02 respectively). In view of the lack of bowel free access, 5 patients underwent PCD catheter insertion via transgastric route. One of these patients required immediate surgery for a colonic fistula with fecal peritonitis secondary to complication caused by PCD insertion. The remaining 4 patients improved with PCD alone. Of the 36 patients in the study, a total of 7 patients (19.4%) suffered PCD complications; of which 3 were in nonsurgical group and four in surgical group. In the non-surgically managed group, one patient developed bile leak from the PCD. A cavitogram revealed a duodenal fistula. This problem was managed by withdrawal of the PCD by a few centimeters. Two other patients in the same group had transgastric pigtail insertion in which the pigtail had slipped into the stomach; these complications were managed by reposition of the PCD. Two patients developed colonic fistula with one patient developing peritonitis who needed immediate surgery as described

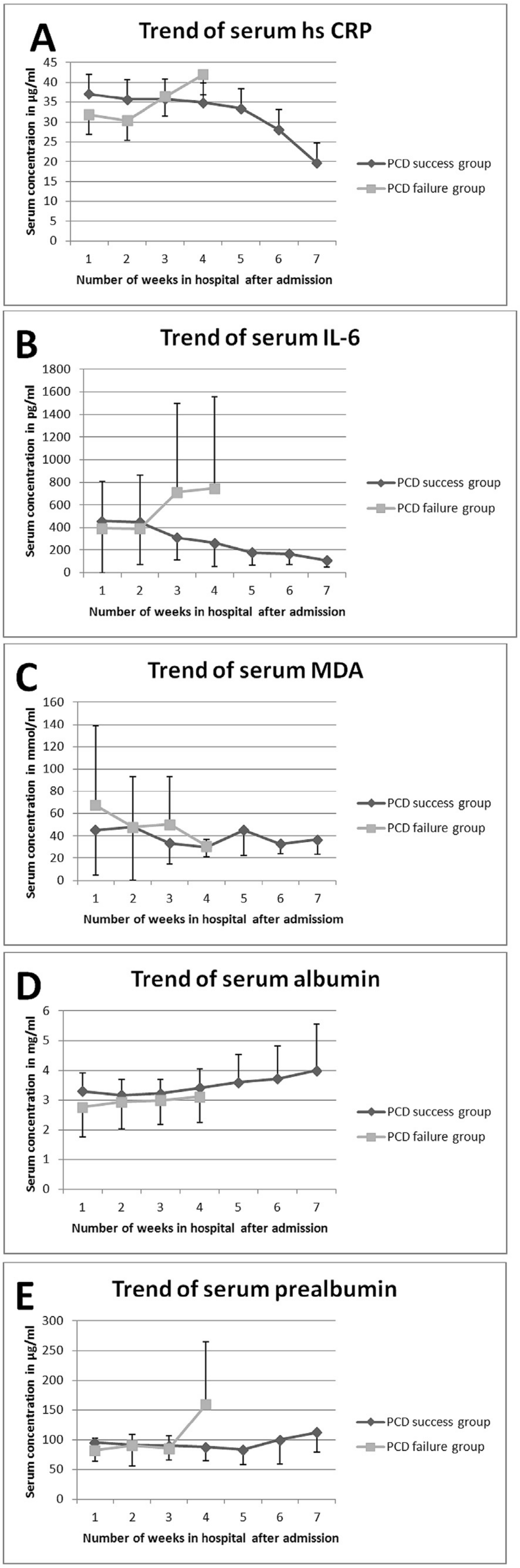

Fig. 1. Graph showing trend of hsCRP (**A**), IL-6(**B**),MDA(**C**),Albumin(**D**) and Pre-albumin(**E**) in patients managed non surgically(n = 18) and in patients managed surgically(n = 6). (Weeks after hospital admission along x-axis and serum concentration along y-axis).

above. The other patient had a feculent discharge from the PCD which was initially managed by gradual withdrawal of the PCD. Later, he had worsening of sepsis for which he underwent necrosectomy. Two patients developed bleed through the PCD catheter. One patient needed exploratory laparotomy and packing due to hemodynamic instability. Intraoperatively, diffuse bleeding was noted in peripancreatic region. The second patient underwent CT angiography which did not reveal any source of the bleed and the patient was managed non-operatively.

3.9. Pancreatic necrosectomy

Of the 11 patients for whom a necrosectomy was indicated, the procedure was actually performed on seven patients (Table 8). Of these 7 patients, one patient had PCD-induced colonic perforation with peritonitis and one patient developed a bleed through the PCD. The remaining 5 patients underwent necrosectomy for persistent or worsening sepsis despite presence of multiple PCDs to drain all collections, administration of antibiotics based on culture sensitivity, and treatment with antifungal when indicated. In another 4 patients, the decision was made to operate in order to manage persistent sepsis. Two of these patients became hemodynamically unstable before surgery could be performed and expired subsequently. The other two patients did not give consent for surgery and left the hospital against medical advice, in critical condition, in spite of repeated counseling regarding the urgent need for surgery.

The mean interval between pain onset and surgical intervention was 65.7 ± 17.9 days, while the mean interval between the 1st PCD insertion and surgical intervention was 41 ± 16.15 days. The mean duration between the 1st PCD and surgery in patients who survived was 62.5 days compared to 70 days for those who did not survive surgery. Six of 7 patients underwent pancreatic necrosectomy, 3 by intraperitoneal approach and 3 by retroperitoneal approach. One patient underwent incision and drainage of collection extending into the scrotum.

In addition, one patient who was reexplored for bleeding through drains following retroperitoneal necrosectomy expired in the immediate postoperative period due to multiorgan failure. Another patient with colonic perforation peritonitis due to PCD developed enterocutaneous fistula from proximal jejunum after necrosectomy. He was managed conservatively but succumbed to persistent sepsis. A third patient developed colonic fistula due to drain erosion and expired due to ongoing sepsis and failure to thrive 16 months after surgery (Table 8).

3.10. Mortality

Excluding the aforementioned two patients who refused further treatment and left the hospital, mortality rate for the remaining 38 patients in the study was 8/38 (21%). Two of 24 patients (8.3%) expired while on a **"Step-up approach with intention to avoid surgery"** before the decision for necrosectomy was made. Three of 7 patients (42.8%) expired after necrosectomy. Thus, the total mortality in patients who underwent a **"Step-up approach with intention to avoid surgery"** was 5/33(15.1%) excluding the two patients who refused surgery and the one who opted for early surgery after PCD.

Table 7
Details and comparison of PCD characteristics.

	Total (n = 36[a])	Non surgical group (n = 24)	Surgical group (n = 11)	p value
Pain onset to 1st PCD interval (days)				
Mean ± SD	35.28 ± 33.9	38.9 ± 38.8	29 ± 21	0.224
Median(Range)	26(3–200)	27.5(3–200)	22(10–80)	
PCD catheter number				
Total numbers	84	49	29	
Mean ± SD	2.17 ± 1.27	1.91 ± 1.24	2.64 ± 1.28	
Median(Range)	2(1–5)	1(1–5)	2(1–5)	0.091
PCD catheter duration (days)				
Mean ± SD	45.4 ± 36.7	56.7 ± 44	31.1 ± 18.9	
Median(Range)	39(2–150)	48(10–150)	27.5(2–60)	0.138
Total PCD procedures	128	84	40	0.138
Mean ± SD	3.44 ± 2	3.33 ± 12.23	3.64 ± 1.56	
Median(Range)	3(1–10)	3(1–10)	4(1–6)	
Trans Gastric PCD insertion	5(13.9)	4(16.7)	1(9.1)	0.491
PCD complications				
Colonic fistula	3(8.3)	0	3(27.2)	0.01
Bleed through PCD	2(5.4)	0	2(18.1)	
Slippage of Transgastric PCD into stomach	2(5.4)	2(8.3)	0	
Duodenal fistula	1(2.8)	1(4.2)	0	

[a] One patient who was improving on PCD alone opted for surgery and thus excluded from final analysis.

Table 8
Details of patients undergoing surgery after PCD.

Age in yrs/ Sex	APACHE II score at admission	APACHE II score at first intervention	Number of organ failed	Time between onset of Pancreatitis and 1st PCD, in days	Time between 1st PCD and surgery, in days	Indication for surgery	Amount of necrosis in grams	Postop outcome	Post op complication	Cause of death	Duration between surgery and death
30/M	9	9	1	53	96	Persistent/ Worsening sepsis	700	Died	Colonic fistula	Ongoing sepsis, MOF	11months
50/M	8	5	2	21	74	PCD complication- colonic perforation	500	Died	ECF, Burst abdomen	Ongoing sepsis, MOF	4months
30/M	15	15	1	24	62	Persistent/ Worsening sepsis	100	survived	Wound infection	–	
28/M	6	9	1	22	70	Persistent/ Worsening sepsis	500	survived	None	–	
32/M	11	11	1	30	40	Bleeding through PCD	500	Died	none	Bleeding, Ongoing sepsis, MOF	2days
27/M	17	15	2	10	68	Persistent/ Worsening sepsis	100	survived	None	–	
24/M	10	10	1	10	50	Persistent/ Worsening sepsis	400	survived	None	–	

3.11. *Factors affecting outcome*

A univariate analysis indicated that etiology, APACHE II at admission, hypocalcemia at admission, length of ICU stay, number of organ failed, late onset organ failure and extrapancreatic necrosis in left anterior and left posterior pararenal spaces were significant factors affecting the outcome of the " step up approach with intention to avoid surgery". A multivariate analysis found none of these factors to be significant.

4. Discussion

The present study was designed to randomize patients into a **"Step-up approach as a bridge to surgery"** and a "**Step-up approach with intention to avoid surgery**". After first block of 4 patients each, we realized that mortality was higher in the **"Step-up approach as a bridge to surgery"** and patients randomized to this group opted out of the study, although they had initially indicated a willingness to participate. As a result, it took us 6 months to complete first 2 blocks of patients. We had to exclude those patients who continued to be hemodynamically unstable and were not fit for surgery. Keeping in view the difficulties of recruitment and retention, which resulted in poor progress, the Surgical Gastroenterology division review committee decided to discontinue the **"Step-up approach as a bridge to surgery"** while proceeding with the "**Step-up approach with intention to avoid surgery**". Though open necrosectomy had been used in both groups, the use of open necrosectomy in patients managed by the **"Step-up approach as a bridge to surgery"** may have led to higher physiological insult in patients who were still recovering compared to the second group. One valid criticism of the study could be that we stopped randomization too soon. However, given the higher mortality in the **"Step-up approach as a bridge to surgery"** group and severe criticism from our department during the weekly Mortality & Morbidity meetings especially when compared to results detailed in our previously published work where the curative efficacy of PCD alone was 48%, with an overall mortality rate of 24% the decision was made to discontinue randomization.

All subsequent patients in the present study were therefore managed with a "**Step-up approach with intention to avoid surgery**". Of the evaluable 35 out of 36 patients, 24 patients (68.5%) were managed by PCD alone including use of multiple PCDs, frequent interventions, aggressive irrigation and close monitoring. This success rate was higher than the previously reported prospective studies [2,7]. More significant is the fact that the current group of patients was sicker at the outset of the study since it included only those patients who failed to show clinical improvement after 10 days of treatment with PCDs.

4.1. Timing of surgery

In the present study, interval between pain onset to surgery was 65 days whereas the interval between the first PCD and surgery was 43 days (Table 7). When compared to the data reported in the study by Babu etal [3], there was an increase in the interval between the onset of symptoms to surgery and first PCD to surgery (65 vs 46 days and 43 vs 27days, respectively). There was an increase in the percentage of patients managed by PCD alone from 48.2% to 68.5%. In the PANTER trial [2], timing between PCD and surgery ranged from 1 to 52 days with a median of 10 days. In a multicenter study by the Dutch pancreatitis study group [8], the median was 10 days with a range of 5–22 days. In both studies, the success rate of PCD was lower (around 35%). Based on our study and available literature, we predict that with additional experience in treating patients with "**Step-up approach with intention to avoid surgery**" the need for surgery in a large percentage of this subgroup of patients may be obviated. This could also be the learning curve effect.

4.2. Outcome in patients managed by PCD and surgery

In the present study, the mortality rate in patients undergoing surgery after a "**Step-up approach with intention to avoid surgery**" was 43% (3 out of 7 patients) which compares favourably with the mortality rate reported in our previous study [3]. By contrast the mortality rates reported in the PANTER study [2] were 23% and 54.5% in study by Zerem et al. [9].

4.3. PCD characteristics and outcome

The average number of catheters used per patient in the present study was 2.17 ± 1.27, which is higher than reported previously [2,7,8]. We hypothesize that the higher number of percutaneous catheters used along with wider bore and frequent upsizing to ensure better irrigation and drainage led to a higher success rate in the present series.

Two of 24 patients (8.3%) expired while on a **"Step-up approach with intention to avoid surgery"** before the decision for necrosectomy was made. Both patients were on PCD for more than 4 weeks, during which time they showed no significant change in condition. They subsequently developed late onset organ failure with rapid deterioration and became hemodynamically unstable before surgery could be performed. In a study by Hovarthet al [10], 17% of patients managed by PCD developed late onset organ failure and 7.8% of the patients managed by PCD expired. Similar mortality was reported in our previous study also (6.8%) [3].

4.4. Factors predicting PCD outcome

A univariate analysis indicated that the factors predicting failure of PCD include alcoholic pancreatitis, hypocalcemia at admission, APACHE II score at admission, duration of ICU stay, number of organs failed, late onset organ failure and presence of extrapancreatic necrosis in left anterior and posterior pararenal space. Alcoholic pancreatitis and hypocalcemia at admission are known predictors of severity of disease, while in the present study they have been found to be significant factors associated with the need of surgery. Between the two groups the difference in the need for mechanical ventilation was significantly different ($p < 0.001$) while the difference in occurrence of persistent respiratory failure or pleural effusion was not different. This finding can be explained by the fact that respiratory failure which did not require mechanical ventilatory support was reversible with PCD insertion and saline irrigation. Thus, in the present study, patients who needed surgery were sicker on admission, had a higher incidence of organ failure and longer ICU stays compared to patients who did not need surgery.

In the present study we observed that the left anterior and posterior pararenal were significantly associated with the need for surgery which has not been reported earlier. This observation may be explained by the fact that the extension of necrosis and infection to perinephric fat is difficult to drain by PCD because there is limited space available, therefore, placement and retention of PCD catheters is difficult.

Late-onset organ failure remains the Achilles heel in the **"Step-up approach with intention to avoid surgery"**. In the present study, 8 patients (22.2%) developed late-onset organ failure while 7 of 8 patients (87.5%) needed surgery. This complication manifested rather suddenly and worsened rapidly, leading to rapid deterioration and little time for intervention.

4.5. Inflammatory and nutritional markers

To our knowledge this is the first study to assess the role of inflammatory and nutritional markers in predicting need of surgery in patients managed by **"Step up approach with intention to avoid necrosectomy"**. We noticed a trend of falling hs-CRP and IL-6 in patients in whom surgery could be avoided, indicating reversal of sepsis. However, MDA values that did not show any definite trend although the initial and last median MDA levels were higher in patients who needed surgery.

Of the two nutritional markers: albumin and prealbumin studied, we observed that levels of serum albumin showed a rising trend in patients who did not need surgery. They also had higher baseline serum albumin and a higher value at 4 weeks. Patients who needed surgery also showed a rising trend in serum albumin but they had a low baseline albumin and slower rise in albumin. Rising serum albumin is indirect evidence of a reversal of the catabolic phase and the presence of the anabolic phase of recovery from illness. Serum prealbumin did not show any particular trend in either group. None of these observations reached statistical significance. A larger study is recommended to clarify the role of inflammatory and nutritional markers in predicting outcome of a step-up approach.

This study has some limitations. Apart from the early discontinuation of the randomized controlled study, the authors belong to a medical care center which aggressively promotes a **"Step-up approach with intention to avoid necrosectomy".** The number of patients included in the present study is small and only includes a difficult subgroup of patients not responding to PCD within 10days of its insertion. Due to financial reasons, inflammatory and nutritional markers were measured in a limited number of patients and only once per week. Daily measurement of these markers would have provided a larger data set.

5. Conclusion

In the present study, randomization into surgery at a predetermined time in a step-up approach was discontinued due to poor progress. A ″**Step up approach with intention to avoid surgery"** led to a success rate of 68.5%, despite the fact that the study included patients who did not show an initial response to PCD. While the timing of surgery after PCD could not be predicted with pinpoint accuracy, the results of the study suggest that a higher percentage of patients can be successfully managed without surgery by an experienced team trained in this approach. Patients who required surgical intervention were found to be sicker on admission, had a higher incidence of organ failure, spent more time in the ICU compared to the patients who did not need surgery. Inflammatory and nutritional markers for identification of patients who are not responding to PCD may also play a role in determining the timing of surgery.

Conflict of interest disclosure

None.

Declaration of funding

Nil.

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