



Assessing the Efficacy and Outcomes Following Irrigation with Streptokinase Versus Hydrogen Peroxide in Necrotizing Pancreatitis: A Randomized Pilot Study

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Abstract

Background Percutaneous catheter drainage (PCD's) are prone to blockage because of necrosum. To improve the efficacy of PCD, necrolytic agents have been used. The present study compared the use of Streptokinase with H₂O₂ in saline irrigation.

Materials and Methods This is a single-center randomized pilot study (from July 2018 to Dec 2019). Patients with infected pancreatic necrosis not showing response to PCD and saline irrigation were included in the study. Patients received either Streptokinase (Streptokinase group 50,000 IU in 100 ml normal saline) or 3% H₂O₂ (3% H₂O₂ in 100 ml normal saline in 1:10 dilution). Primary endpoints were the need for surgery and mortality while secondary endpoints were hospital stay and complications attributable to necrolytic agents.

Results There were 30 patients in the study, 15 in each arm. Organ failure was seen in 23 (76.6%), single organ failure was present in 11 (47%), and multi-organ failure in 12 (53%). Bleeding complications (20% in H₂O₂ vs 6.6% in Streptokinase), need for surgery (73% in H₂O₂ vs 33.3% in Streptokinase) and mortality (60% in H₂O₂ vs 33% in Streptokinase) were higher in H₂O₂ group but the difference was not significant statistically. Post-irrigation hospital stay was lesser in the Streptokinase group compared to H₂O₂ group but the difference did not reach statistical significance (14.1 ± 7.7 vs 19.2 ± 11.7, *p* = 0.09)

Conclusions Streptokinase irrigation led to a trend for reduced need for necrosectomy and mortality. H₂O₂ group had more bleeding complications. Post-irrigation hospital stay was lesser in Streptokinase group.

Keywords Necrotizing pancreatitis · PCD failure · Irrigation with streptokinase · Irrigation of cavity with hydrogen peroxide

Introduction

Traditionally infected pancreatic necrosis has been managed with surgical necrosectomy and antibiotics (1). However, the step-up approach in the PANTER trial leads to a paradigm shift in the use of percutaneous drainage as a bridge to

definitive therapy (2). Our results with the use of PCD as a definitive therapeutic modality have been variable from 48 to 66% using vigorous saline irrigation (3, 4). However, the major reason for the failure of PCD as a definitive therapy is the predominance of solid necrosum, which leads to frequent blockage of PCD and makes it less effective (5, 6). The use of PCD as a definitive modality is associated with reduced incidence of new-onset organ failure, lower rate of incisional hernia, and lower incidence of diabetes mellitus (2, 7–9). To improve the patency of PCD and to hasten necrolysis of solid necrosum, various modalities have been used (3, 10). The most commonly used modality is large volume saline irrigation (3). Our group has published results with the use of Streptokinase to enhance the success of PCD in patients not responding to saline irrigation (10–12). It was proposed that Streptokinase acts by fibrinolysis of necrosum and leads to its dissolution by acting on the surface of necrosum (10).

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Its role in the management of empyema thoracis and a liver abscess is already reported (13).

Hydrogen peroxide is another solution that has been used in the necrotic cavity to clear the necrotic debris. Abdelhafez et al. in a series of 10 cases who underwent Trans luminal retroperitoneal endoscopic necrosectomy (TREN) reported improved results with hydrogen peroxide irrigation in the necrotic cavity (14). In a study by Othman et al., complete cavity resolution was seen in 95% of the patients with extended cysto-gastrostomy (15). The possible reason for such results might be the facilitation of necrotic tissue dislodgement, debridement, and ease of debris extraction during an endoscopic intervention. Though intervention gastroenterologists continue to use H₂O₂, its role in cavity irrigation through PCD is still not evaluated.

In the present study, we planned to compare the efficacy of Streptokinase with hydrogen peroxide as necrolytic agents in improving drainage and the success of PCD.

Methodology

Trial Design

The present study was a single-center randomized pilot study conducted in Departments of Surgical and Medical Gastroenterology between July 2018 to December 2020. This study was approved by Institutional Ethical Committee and registered in the clinical trials registry of India (CTRI/2019/02/017633) and the study was performed as per Helsinki declaration 1961. Informed consent was taken from all the participants as per Helsinki guidelines.

Trial Population

Patients above 18 years with necrotizing pancreatitis requiring PCD were evaluated and those without significant symptomatic and radiological response 72 h after PCD drainage and saline irrigation were included in the study. Percutaneous drainage was done by experienced intervention radiologists under ultrasonographic/CT guidance. Initially, 10-14F pigtailed drains were placed, according to size and nature of the collection, and were upsized as required. We excluded patients undergoing emergent surgical necrosectomy, allergic to Streptokinase, deranged coagulation profile, the recent history of cerebrovascular accident (CVA), who underwent intracranial or spinal surgery, and those with uncontrolled hypertension and intracranial neoplasm.

Interventions and Outcomes

In the Streptokinase group, 50,000/150,000 IU of Streptokinase was diluted with 100 ml normal saline and given

through PCD for 60 min and then PCD was clamped for 30 min. After the release of a clamp, the cavity was irrigated with 200 ml of normal saline instilled over 2–3 h. In the hydrogen peroxide group, 10 ml of 3% Hydrogen peroxide diluted with 100 ml of normal saline (1:10 dilution) was given through the PCD. PCD was clamped for 30 min and this was followed by irrigation with 200 ml of saline over 2–3 h. Hydrogen peroxide and Streptokinase irrigation were given 3 times a day for 3 days followed by an assessment of the clinical and biochemical parameters. Surgery in the form of minimal incision surgery /open necrosectomy or VARD was done if the patient did not show clinical improvement after irrigation, i.e., persistent sepsis, worsening, or new-onset organ failure, persistent unwellness, uncontrolled hemorrhage). The primary endpoints of the study were the need for surgery and mortality, while secondary endpoints were the length of hospital stay, safety, and complications associated with Streptokinase and hydrogen peroxide irrigation.

Sample Size

It was a non-inferiority trial and the objective of the study was to compare the efficacy, safety, and complications of hydrogen peroxide with Streptokinase. The sample size of 15 was used to test each arm and was calculated as per the methods given by Browne et al. (16).

Randomization

Eligible patients who met inclusion criteria were enrolled in the study. Once PCD was placed, patients were assessed for proper positioning of the catheter and adequate drainage of the cavity. Sometimes more than one catheter was required to ensure adequate irrigation. All these patients underwent saline irrigation for at least 72 h and were reassessed for the clinical, biochemical, and radiological response. If there was no improvement clinically, then these patients were randomized to either the Streptokinase or hydrogen peroxide group. Randomization was done using computer-generated random numbers. After generating random numbers, patients were allocated to either group by the principal investigator.

Blinding

Patients and principal investigator were blinded. However, medical and nursing staff including investigator (Dr Venu Bhargava) responsible for giving irrigation could not be blinded as it was difficult to conceal the effervescence of hydrogen peroxide in pigtail drains from the treating staff.

Statistical Analysis

SPSS version 23 was used for analyzing the data. Parametric data were expressed as mean \pm S.D. For comparison between two independent groups for a continuous parametric, variable an independent t test was applied and for a nonparametric variable, the Mann–Whitney U test was applied. For comparison between two independent groups for a categorical variable chi-square test was applied. Univariate and multivariate analyses were done by logistic regression scale, a *p* value of < 0.05 was considered significant.

Results

A total of 48 patients were assessed, of which 18 were excluded as 10 underwent endoscopic necrosectomy, six underwent upfront trans-gastric necrosectomy and two had surgery for hemorrhage. The remaining 30 patients were included in the study of which 15 patients received Streptokinase and 15 received hydrogen peroxide (Fig. 1).

There were 22 males and 8 females in the study cohort and were equally distributed in two arms. The mean age of the cohort was 36.5 ± 10.4 (range 18–52) years and it was comparable between the two groups. Alcohol and gall stones were the most common etiologies. Organ failure at first intervention was noted in 23 (76.6%) patients and was comparable in the two groups. Mean Modified Marshall score at presentation was higher in the Streptokinase group compared to the hydrogen peroxide group, however, the difference was not significant (4.2 ± 2 vs 3.6 ± 1.9 , $p = 0.8$). The mean APACHE II score in the present study was 10.7 ± 5.2 and was higher in the Streptokinase group compared to the H₂O₂ group (12.8 ± 4.8 vs 11.6 ± 5.5). Ventilatory support was required in 63% of the patients before irrigation (60% in Streptokinase vs 67% in hydrogen peroxide). Two groups were comparable in terms of the number of PCDs used, positive drain culture, interval between onset of pain to PCD insertion, onset of pain to surgery, interval after irrigation to surgery. (Table 1).

Comparison of Sepsis Reversal and Organ Failure Reversal Post-irrigation Between Groups

Sepsis reversal was seen in 7 and 6 patients respectively in streptokinase and H₂O₂ group and reversal of organ failure was seen in 8 and 7 patients respectively and difference was not significant. 11/30 patients were successfully managed with PCD alone in this cohort, out of which 9 were in Streptokinase group and 2 in H₂O₂ group, though the difference was not statistically significant ($p = 0.3$). In the entire cohort,

new-onset organ failure was seen in 3 patients of which one was in the Streptokinase group and 2 in the H₂O₂ group (Table 2).

Comparison of Pre- and Post-irrigation Characteristics Between Two Groups

Compared to the pre-irrigation score, there was a significant decrease in post-irrigation mean APACHE II score in the Streptokinase group (12.8 ± 4.8 vs 9 ± 5.2 , $p = 0.02$). However, the decline in H₂O₂ group did not reach statistical significance. MMS score also declined post-irrigation in the two groups, but the difference was not significant. Similarly, there was a considerable drop in procalcitonin levels in both groups but the difference again is not significant (Table 3).

Complications Associated with Irrigation in Both the Groups

Four (13.3%) patients on irrigation had hemorrhage from drains, out of which 1 (6.6%) patient was in the Streptokinase group while 3 (20%) were in the hydrogen peroxide group. One patient in H₂O₂ group required angioembolization. (Table 2).

Eight patients (26.6%) had abdominal distension during irrigation, 3 in Streptokinase group and 5 in H₂O₂ group while 6 (20%) patients had vomiting during irrigation, 3 in each group. Temporary discontinuation of irrigation was required in 6 (20%) patients (Table 2). Post-surgery hemorrhage was seen in 6 (37.5%) patients of which one patient in H₂O₂ group required angioembolization (Table 4).

Comparison of Surgical Parameters Between Two Groups

16/30 patients underwent surgery in the present study. There was no significant difference in the need for surgery in the two groups, 7 (46.7%) in streptokinase group vs 9 (60%) in H₂O₂ group. Minimal incision necrosectomy was performed in 12 patients, trans-gastric necrosectomy in 3 (100%), and video-assisted retroperitoneal debridement followed by minimal incision necrosectomy in one patient. Indication of surgery in all these patients was PCD failure following irrigation. Three patients required two surgeries, one for persistent vomiting which required feeding jejunostomy and tube gastrostomy, one underwent diversion loop ileostomy following necrosectomy with colonic fistula, and one patient required 4 surgeries because of bleeding from the cavity leading to hemodynamic instability (Table 4). Postsurgical complications were comparable between the two groups.

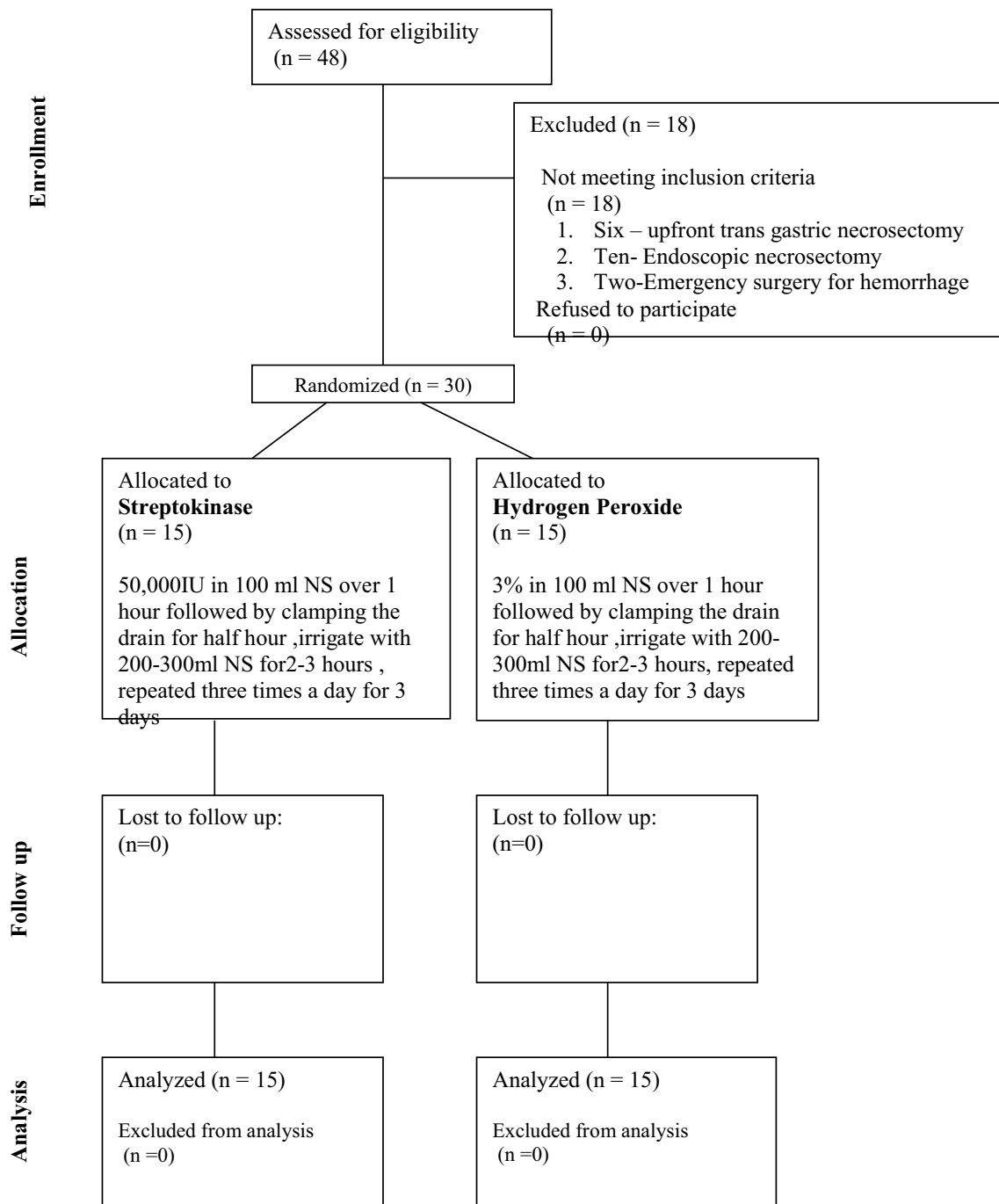


Fig. 1 Flow chart showing patient selection and protocol in both the groups

Mortality

Fourteen (46.6%) patients died in our study. Mortality was lower in Streptokinase group 5 (33%) patients compared to 9 (60%) in H₂O₂ group though the difference was not significant ($p = 0.15$). Postoperative mortality was also lower in Streptokinase group (26.6 vs 46%, $p = 0.5$). We

noted higher mortality in patients with multi-organ failure compared to single organ failure (43.5 vs 13%). Mortality was 21% ($n = 3/14$) in patients managed with PCD alone. However, disease-specific mortality was observed in only one patient in the Streptokinase group managed with PCD alone (Table 4). No mortality was observed in the subgroup that achieved sepsis reversal.

Table 1 Comparison of baseline characteristics between two groups

Variable	Streptokinase group <i>n</i> =	Hydrogen peroxide group <i>n</i> =	<i>p</i> value
Age in years	34.9 ± 9.7 (18–52)	38 ± 11.1 (19–50)	0.26
Sex (M:F)	6.5:1	1.8:1	0.22
Etiology	10 (33%)	6 (20%)	0.43
Alcohol	4 (13.3%)	6 (20%)	
Gall stone	1 (3.3%)	3 (10%)	
Idiopathic			
Total number of Admission	13	12	0.69
1	2	3	
2			
Organ failure, <i>n</i> (%)	12 (40%)	11 (36%)	0.11
Single, <i>n</i> (%)	5 (16%)	6 (20%)	
Multi-organ failure, <i>n</i> (%)	7 (23%)	5 (16%)	
MMS score at presentation	4 ± 2 (1–6)	3 ± 1.9 (0–6)	0.8
APACHE II at presentation	12.8 ± 4.8 (4–17)	11.6 ± 5.5 (1–20)	0.39
Positive drain cultures (<i>n</i>)	9 (30%)	9 (30%)	0.23
No of PCD	1	1	0.47
1	10	12	
2	7	3	
3	3	2	
4			
Size of the PCD	2	0	0.06
12Fr	4	3	
14Fr	1	7	
16Fr	6	5	
18Fr	2	0	
22Fr			
Necrosis % in number of patients	0	1	0.6
< 30%	5	7	
30–50%	10	7	
> 50%			
Interval after irrigation to surgery in days	2.6 ± 3.2 (0–11)	1.7 ± 2.4 (0–7)	0.09
Number of days PCD used	18.6 ± 24.7	34.2 ± 23	0.40
Number of days onset of pain to PCD insertion (median in days)	28	30.50	0.78
Interval from onset of pain to surgery in days	35.2 ± 6.7 (29–130)	31.4 ± 3.4 (28–80)	0.54
Post-irrigation MMS score	3.4 ± 1.8 (0–6)	2.2 ± 1.9 (0–6)	0.89
Post-irrigation APACHE II	9 ± 5.2 (0–17)	9.6 ± 5 (1–17)	.097
ICU stay before irrigation in days	11.3 ± 15.3 (0–44)	9.9 ± 21 (0–75)	0.8
ICU stay after irrigation in days	7.3 ± 6.3 (0–20)	7.13 ± 6.5 (0–20)	0.9
Number of patients on ventilator before irrigation, <i>n</i> (%)	9 (30%)	10 (33.3%)	0.5
Hospital stay before irrigation in days	35 ± 19.7 (7–78)	35.80 ± 27.4 (5–78)	0.8
Hospital stay after irrigation in days	14.1 ± 7.7 (5–36)	19.2 ± 11.7 (0–41)	0.09

On multivariate analysis, factors associated with mortality in the entire study cohort were organ failure and the need for surgery (Table 5).

Discussion

Percutaneous catheter drainage plays an important role in the management of necrotizing pancreatitis. The present study showed that the use of Streptokinase as an adjunct to saline irrigation resulted in a trend for decreased need

for surgery and lower rates of morbidity and mortality compared to H₂O₂ group.

There has been apprehension in the scientific community to use Streptokinase because of the risk of bleeding. However, the incidence of bleeding complications was more in the H₂O₂ group (20 vs 6.6%) even though statistical significance was not achieved. In addition, there was a higher incidence of abdominal distension and the need for temporary discontinuation of irrigation due to abdominal discomfort and distension in the H₂O₂ group compared to Streptokinase.

Table 2 Pre- and post-irrigation characteristics between two groups

Variable	Streptokinase group (n = 15)			Hydrogen peroxide group (n = 15)		
	Pre-irrigation	Post-irrigation	p value	Pre-irrigation	Post-irrigation	p value
Modified Marshall Score	4 ± 2 (1–6)	3.4 ± 1.8 (0–6)	0.301	3.07 ± 1.9 (0–6)	2.2 ± 1.8 (0–6)	0.054
APACHE II score	12.8 ± 4.8 (4–17)	9 ± 5.2 (0–17)	0.029	11.6 ± 5.5 (1–20)	9.6 ± 5.5 (1–17)	0.12
MMS ≤ 2	6	7	0.035	6	4	0.34
Apache II ≤ 8	5	8	0.019	6	4	0.75
Albumin	2.3 ± 0.27 (2–3)	2.31 ± 0.28 (2–3)	0.912	2.18 ± 0.31 (1–3)	2.36 ± 0.38 (2–3)	0.07
Number of CT per patient	2 ± 0.53 (1–3)	1.8 ± 0.6 (1–3)	0.271	2.8 ± 1.4 (1–5)	2.07 ± 0.79 (1–3)	0.06
Number of PCD per patient	1.8 ± 0.67 (1–3)	0.4 ± 0.5 (0–1)	0.04	2.13 ± 0.64 (1–3)	0.4 ± 0.56 (0–1)	0.02
Procalcitonin in IU	14.8 ± 25.5	7.7 ± 10.9	0.226	13.3 ± 25.5 (0–100)	3.4 ± 7.2 (0–28)	0.05
ICU stay in days	11.3 ± 15.3 (0–44)	7.3 ± 6.3 (0–20)	0.231	9.9 ± 21 (0–75)	7.1 ± 6.4 (0–20)	0.62

Table 3 Complications following irrigation between two groups

Complications	Streptokinase group (n = 15)	Hydrogen peroxide group (n = 15)	p value
Bleeding with irrigation, n (%)	1 (3%)-Conservatively managed (no drop in hemoglobin)	1 (3%)-DSA angio embolization of splenic artery 2 (6%)-conservatively managed (no hemoglobin drop)	0.29
Abdominal distension during irrigation, n (%)	3 (10%)	5 (16%)	0.34
Vomiting, n (%)	3 (10%)	3 (10%)	0.67
Required temporary discontinuation, n (%)	1 (3%)-due to hemorrhage	3 (9%)-hemorrhage 2 (6%)- abdominal distension	0.08 (OR-7.00)
PCD alone (n = 3/14), n (%)	1 (3%) (coagulopathy and hemodynamic instability)	2 (6%) (Myocardial infarction in 1 patient) Pulmonary thrombo embolism in one patient)	0.45
Sepsis reversal (n = 15)	7 (46%)	6 (40%)	0.5
Organ failure reversal (n = 15)	8 (53%)	7 (46%)	0.3
New-onset organ failure post-irrigation, n (%)	1 (3%)	2 (6%)	0.24

Table 4 Post surgical complications between two groups

Parameter	Streptokinase group (n = 15)	Hydrogen peroxide group (n = 15)	p value
Minimal incision necrosectomy, n (%)	4 (13%)	8 (26%)	0.14
Transgastric necrosectomy, n (%)	2 (6%)	1 (3%)	0.55
Staged procedure, n (%)	1 (3%)	0	0.32
Postsurgical complications, n (%)	3 (9%)	3 (9%)	1.0
Hemorrhage	1 (3%)	1 (3%)	0.14
Splenic artery embolization	1 (3%)	0	0.34
Re exploration	1 (3%)	1 (3%)	
Conservatively, managed	1 (3%)	0	
Colonic fistula,	1 (3%)	2 (6%)	
Duodenal fistula			
Mortality, n (%)	5/15 (33.3%)	9/15 (60%)	0.15
Mortality following Surgery (n = 11/16)	4/30 (13%)	7/30 (23%)	0.51
Organ failure (n = 13/23)	5 (16%)	8 (26%)	0.48
Single, n (%)	1 (3%)	3 (9%)	
Multiple, n (%)	4 (13%)	5 (26%)	

As stated earlier, superior results in the Streptokinase group might be because of its fibrinolytic action which leads to fragmentation of necrosom at the periphery and complete digestion of supportive collagenous framework in

fragmented necrotic tissue converting it into structure-less masses (2). Life-threatening hemorrhage was not observed in any patient in the Streptokinase group and it has been reported previously that Streptokinase does not affect tunica

Table 5 Factors predicting mortality

Variable	Streptokinase group (<i>n</i> = 15)		Hydrogen peroxide group (<i>n</i> = 15)	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
ICU stay	<i>p</i> = 0.042	<i>p</i> = 1.00	<i>p</i> = 0.001	<i>p</i> = 0.04
Need for invasive mechanical ventilation	<i>p</i> = 0.025	<i>p</i> = 1.00	<i>p</i> = 0.02	<i>p</i> = 0.09
Organ failure	<i>p</i> = 0.73	<i>p</i> = 0.46	<i>p</i> = 0.004	<i>p</i> = 0.01
Need for surgery	<i>p</i> = 0.077	<i>p</i> = 0.34	<i>p</i> = 0.001	<i>p</i> = 0.065

adventitia, media, or intima (17). On the other hand, hydrogen peroxide acts by conversion into water and nascent oxygen. Release of nascent oxygen and heat probably lead to abdominal discomfort and distension which led to temporary discontinuation of irrigation.

Othman (15) et al. performed endoscopic trans-gastric cysto-gastrostomy and they irrigated the cavity by endoscopic trans-gastric route with 30 cc of 3% hydrogen peroxide in 1:1 concentration. The radiological resolution of the cavity was seen in 63% over 3 months. However, in our study, we used a more dilute form of hydrogen peroxide 3% (1:10) as there was no study available on its use through percutaneous drains in necrotizing pancreatitis. We found that at this dilution also, the frothing and heat generation was brisk. It is a well-known fact that hydrogen peroxide releases local heat during the chemical reaction, and we believe that release of local heat in addition to the release of nascent oxygen may be contributing to the removal of adherent necrotic tissue.

The success of PCD has been variable from 35 to 84% in different studies (1, 2, 9). In the PANTER trial (2), the success rate of PCD alone with the step-up approach was 35%. In our previous study, we noted the success rate of 48% with PCD alone using large volume saline irrigation and noted sepsis reversal in 62.5% of the patients (3). However, the present study is different from our previous study as we had included a subset of patients with pancreatic necrosis who did not show response to PCD and saline irrigation. Therefore, this is the subset of patients requiring further step up to surgical intervention, and in this subset, we noted a success rate of 36.6% using PCD alone with Streptokinase and hydrogen peroxide. We noted a lower incidence of necrosectomy in the Streptokinase group in comparison to the H₂O₂ group (33 vs 73%) though the difference was not significant. In addition, patients treated percutaneously with Streptokinase had a higher success rate with PCD compared to hydrogen peroxide (60 vs 13%). It is important to highlight that all these patients were otherwise candidates for surgery.

In previous studies presence of organ failure was observed as the single most important factor predicting

mortality (3, 4). These authors had noted that mortality with multi-organ failure was higher compared to single organ failure (8–20 vs 40–70%) (18) (19). Multi-organ failure was previously reported in 35–65% of severe acute necrotizing pancreatitis (2, 3, 20). However, in the present study, we noted organ failure in 77% of patients and multi-organ failure in 40% of patients. Nineteen (63%) patients required invasive mechanical ventilation at first intervention. In previous studies, organ failure reversal following PCD insertion has been reported between 19 and 35% (3, 20), compared to 53% in the Streptokinase group and 46% in the H₂O₂ group (*p* = 0.33) in the present study.

In the present study, we also noted that determinants of severity like MMS score > 2, APACHE II score, APACHE II > 8, and serum procalcitonin levels decreased in both groups post-irrigation. However, we noted that the decline of severity was significant in the Streptokinase group compared to the hydrogen peroxide group. We did not find a significant difference in ICU stay and total length of stay between the two groups.

The disease-specific mortality following necrosectomy has been reported from 20 to 50% among various studies (2, 3, 9, 21). 47% of patients died in our study, and mortality was higher in the H₂O₂ group compared to the Streptokinase group 9 (60%) vs 5 (33%), though the difference was not significant (*p* = 0.153). This may be attributed to significant decline in disease severity post-irrigation in streptokinase group. (Table 3).

Limitations of the study include that only patients and principal investigator were blinded while research investigator and rest of team were aware of the protocol used for patients which can lead to bias. Moreover, number of patients was another limitation. We did see clear trends but no significant differences in two treatment arms.

In conclusion results of our study show that use of Streptokinase lead to a trend of decreased need for surgical necrosectomy, lower morbidity, and mortality in comparison to H₂O₂ in this non-inferiority trial. A multicenter trial with large numbers is required to establish the efficacy and superiority of one agent over the other in necrotizing

pancreatitis before we can recommend use of streptokinase in endoscopic necrosectomy.

Declarations

Conflict of interest The author reports no conflict of interest and has no financial disclosures concerning this manuscript.

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