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Early selective enteral feeding in combination with active decompression of duodenum in treatment of moderate and severe acute pancreatitis – A proof-of-concept clinical study

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ABSTRACT

Background: Acute pancreatitis (AP) is a significant clinical challenge with rising global incidence and substantial mortality rates, necessitating effective treatment strategies. Current guidelines recommend pain and fluid management and early enteral feeding to mitigate complications, yet optimal feeding route remains debated.

Methods: We conducted a prospective, randomized, controlled trial at nine centers from October 2020 to May 2023, enrolling 154 patients with moderate to severe AP. Patients were stratified into biliary and non-biliary categories and randomized 1:1 to receive either standard of care (SoC) or SoC plus PandiCath®, a novel catheter enabling selective enteral feeding and duodenal decompression. The primary clinical endpoint (PCE) was a composite of *de novo* multiple organ dysfunction syndrome (MODS), infectious complications, pancreatic and intestinal fistula formation, bleeding, abdominal compartment syndrome, obstructive jaundice, and AP-related mortality.

Results: In the primary modified intention-to-treat analysis, PandiCath® significantly reduced the PCE compared to SoC alone (P = 0.032). The Relative Risk (RR = 0.469, 95 % CI 0.228–0.964) and Number Needed to Treat (NNT = 6.384, 95 % CI 3.349–68.167) indicated its substantial clinical benefit, primarily driven by reduced rates of *de novo* MODS and infectious complications. These findings were further supported by the evaluation of other populations, including the standard intention-to-treat analysis.

Conclusion: PandiCath®, facilitating targeted enteral feeding while isolating and decompressing the duodenum, demonstrates promise in improving outcomes for AP patients at risk of severe complications. Further studies are warranted to validate these findings and explore optimal timing and patient selection for this intervention.

1. Introduction

Acute pancreatitis (AP) is a prevalent medical condition, with a global incidence of ~2.6 million cases annually [1], showing a persistent upward trend. In the USA alone, emergency department visits for AP increased by 18 % from 2006 to 2014 [2] and by an additional 9 % to 2018 [3]. In 20–25 % of cases with moderate to severe disease, mortality rates can reach 35 % [4–6] primarily due to infectious complications and multiple organ dysfunction syndrome (MODS). According to the WHO, AP ranks as the 14th leading cause of mortality globally [7], with rates ranging from 0.90 to 1.10 per 100,000 population [1,2].

Early initiation of enteral feeding is recognized as a key factor in improving the outcomes for patients with AP by avoiding the reduction of intestinal lymphoid tissue and reducing the incidence and severity of infectious complications [8,9]. Thus, international treatment guidelines for AP recommend intensive therapy combined with gastric and intestinal drainage and early enteral feeding [10]. However, consensus is lacking on the optimal route for enteral nutrition administration — oral, gastric, or intestinal [8,10,11].

While enteral feeding provides benefits, it can also stimulate the continuous production of cholecystokinin and secretin in the

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duodenum, along with neurogenic vagal hyperstimulation of exocrine function, which are known triggers of AP [11–14]. Additionally, duodenal dilation or dysfunction of major duodenal papillae can impede the outflow of bile and pancreatic juice. This could lead to the reflux of duodenal contents and bile acids into the pancreatic duct, potentially causing AP [15–19]. Intestinal paresis can cause stasis, disrupt barrier function and promote the proliferation and movement of bacteria and bacterial products across the mucosa. This can lead to bacterial overgrowth and the seeding of adjacent tissues [20], accompanied by the release of inflammatory mediators from the small bowel [21]. Clinically, reduced duodenal motility is associated with an increased risk of pancreatitis developing infectious complications [20–26].

Considering these factors, an effective treatment strategy for AP could involve selectively administering enteral feeding while simultaneously protecting the duodenum from the passage of gastric and reflux of intestinal contents. This approach would also incorporate active duodenal decompression with drainage of both the stomach and intestine. Such a strategy would provide the benefits of enteral feeding while reducing the stimulation of pancreatic exocrine function and concurrently managing the adverse effects of duodenal paresis.

We developed the PandiCath® catheter for this purpose [27,28]. It isolates the duodenum from the stomach and jejunum using inflatable balloons, allowing selective delivery of enteral nutrition into the proximal jejunum. Simultaneously, it drains the stomach and proximal intestine, thus reducing luminal contents including bacteria and intestinal secretions, and actively decompresses the duodenum. Additionally, the catheter enables local administration of medications directly into the duodenum.

Selective enteral feeding combined with active drainage and duodenum decompression using PandiCath® has been shown to effectively treat an AP patient at high risk of progression to a severe or fatal condition [28]. Here, we present the results of a randomized prospective trial of standard of care (SoC) with or without PandiCath® for treating moderate and severe AP.

2. Patients and methods

2.1. Study design, enrollment and randomization procedure

A prospective, randomized, controlled, stratified, open-label, multicenter study was conducted at nine clinical centers from October 2020 to May 2023. The list of participating clinical centers is provided in Supplementary File: Table S1. The Institutional Review Boards of participating clinical centers approved the study protocol and the Informed Consent Form (ICF). Patients with suspected AP were pre-screened shortly after admission using the Working Group IAP/APA Acute Pancreatitis Guidelines, 2013 criteria [11]. The center investigators evaluated those patients meeting primary criteria and consenting to participate in the study. The study team assessed screening information provided by investigators and determined eligibility for enrollment. Patients meeting the study's enrollment criteria were stratified into biliary and non-biliary pancreatitis categories. Each category was then randomly assigned in a 1:1 ratio using a pre-established block-randomization table into Group 1 – PandiCath® + SoC, and Group 2 – SoC alone. SoC corresponded to the Working Group IAP/APA Acute Pancreatitis Guidelines, 2013 [11]. The study design and enrolment and conduct procedures are shown in Fig. 1.

2.2. Study participants

2.2.1. Inclusion criteria

Men and women between 18 and 85 years old could be enrolled in the study within 46 h of hospitalization and ≤94 h after symptoms onset, provided they signed the ICF. They met the criteria of moderate to severe acute biliary or non-biliary pancreatitis according to Atlanta 2012, except as described in the exclusion criteria.

According to the Working Group IAP/APA Acute Pancreatitis Guidelines, 2013, criteria diagnosis of AP was based on any two of the three parameters as follows:

- abdominal pain syndrome;
- serum amylase level more than 3 x the upper limit of normal (i.e. >300 U/L);
- results of abdominal ultrasonography and/or multi-detector computed tomography (mCT) meeting the criteria of AP.

Since the conclusive diagnosis of severe AP is only possible 48 h after hospitalization – beyond the 46-h randomization window allowed in the study, we first aimed to rule out patients with mild AP. Thus, diagnosis of a moderate or severe ("non-mild") AP for enrollment was based on the presence of any of the following conditions:

1. Systemic inflammatory response syndrome (SIRS), score ≥2 in the presence of local complications (see 2 and 3 below) and/or MODS, score ≥2 according to the modified Sequential Organ Failure Assessment (mSOFA), at least at one examination within the first 46 h of hospitalization.
2. Local complications shown by abdominal mCT.
3. Signs of moderate to severe AP revealed by the diagnostic laparoscopy (i.e. intra-abdominal steatonecrosis, enzymatic peritonitis, aseptic peripancreatitis, omentobursitis).
4. Computed tomography severity index (CTSI) score of ≥3 points within 48 h of hospitalization.
5. Bedside Index for Severity in Acute Pancreatitis (BISAP) score of ≥2 points within 24 h of hospitalization.
6. Ranson's score of ≥3 points within 48 h of hospitalization.
7. Acute Physiology and Chronic Health Evaluation II (APACHE II) score of ≥8 points within 48 h of hospitalization.

2.2.2. Exclusion criteria at enrollment

Hereby, we present the findings of a proof-of-concept (PoC) study. Therefore, we excluded patients with conditions that could significantly impact our ability to evaluate the study results objectively. The list of exclusion criteria applied at enrollment is provided in Supplementary File: Table S2. Specifically, we aimed to exclude patients for whom we deemed the use of PandiCath® unlikely to be beneficial. Patients with concurrent conditions that could potentially complicate treatment evaluation or cause harm were excluded. Furthermore, the presence of conditions defining the Primary Clinical Endpoint (PCE) at enrollment was considered an exclusion criterion, except for the presence of MODS.

PandiCath® may be effective even after autolytic inflammation of the pancreas has already been established. However, before irreversible organ and systemic changes occur, earlier application is likely more beneficial. Therefore, we restricted the time window for patient randomization and initiation of treatment with PandiCath® to 46 h and 48 h post-admission, respectively, and 94 h and 96 h post-symptoms onset, respectively.

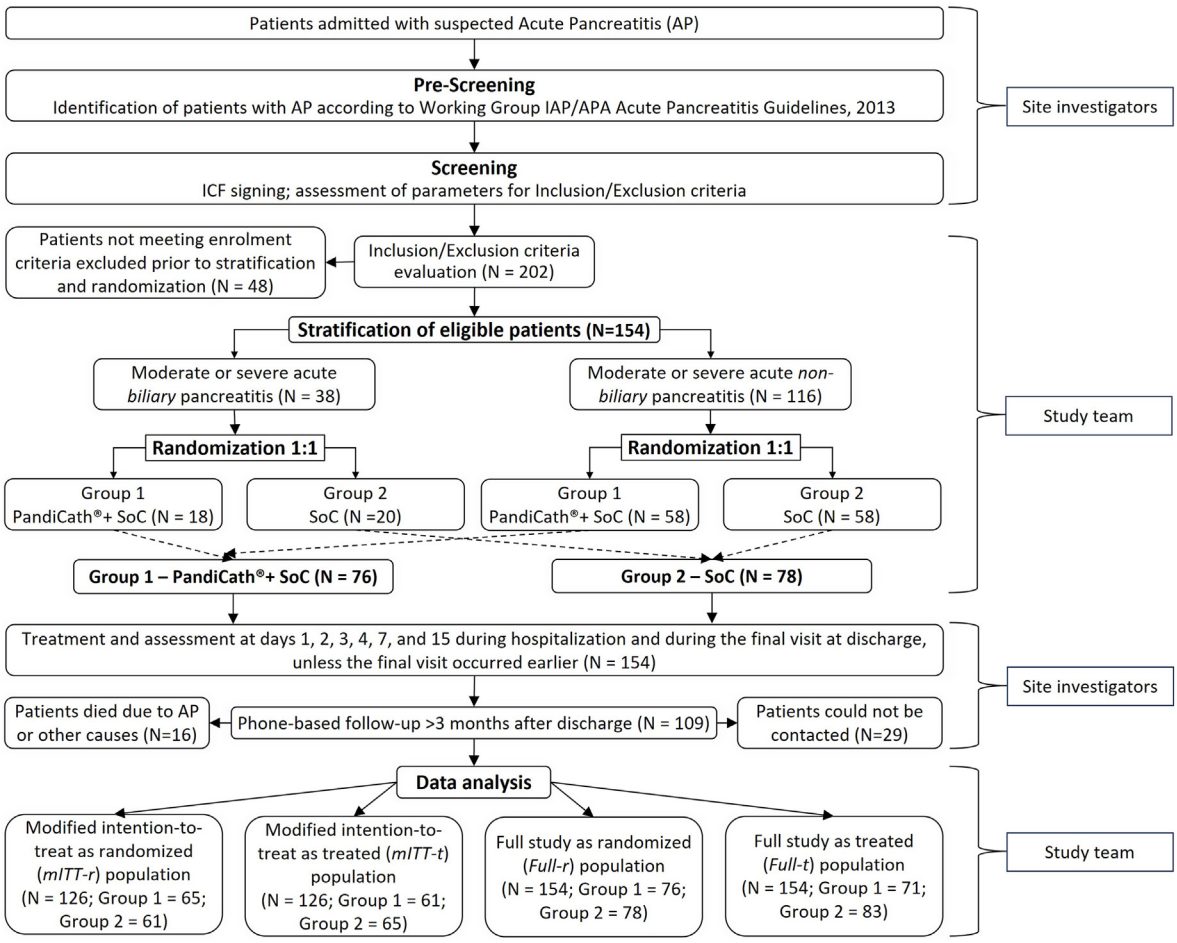

Fig. 1. Proof-of-Concept study design and enrolment and conduct procedures.

2.2.3. Withdrawal criteria

The study was conducted in an emergency department and acute surgical settings, with less than 46 h available for a comprehensive patient evaluation before randomization. Consequently, some patients who still needed to fully meet the inclusion and exclusion criteria were randomized. Additionally, there were instances of protocol deviations during treatment. To address this, withdrawal criteria were formulated in the study protocol (Supplementary File: Table S3). If these criteria were present, the respective patients were removed from the per-protocol (not shown here) and modified intention-to-treat (*mITT*) analysis populations. The most common withdrawal criterion was the breach of study's inclusion and exclusion criteria, which were present before randomization but were not identified during screening. Additionally, conditions that hindered treatment effect assessment, such as those causing events included in the definition of the PCE but unrelated to AP (e.g., iatrogenic complications), were considered. If identified, the withdrawal criteria were consistently applied to both study groups with the intention of retaining as many subjects in the analysis populations as feasible.

2.3. Interventions

All enrolled patients received standard of care per the Working Group IAP/APA Acute Pancreatitis Guidelines, 2013, including pain and fluid management and early enteral feeding. In SoC Group 2, enteral feeding was administered using peroral, nasogastric, or nasojejunal routes. Patients in Group 1 received selective enteral feeding via the PandiCath® catheter, which also isolated and decompressed the duodenum. PandiCath® was placed endoscopically, with the radiological confirmation of correct positioning. PandiCath® was utilized with inflated balloons and negative pressure continuously for up to 48 h or until gut peristalsis was restored. Patients were deemed to have received the correct experimental treatment with PandiCath® if they met all specified criteria:

1. Correct duodenal positioning of PandiCath®;
2. Proper use of experimental treatment equipment, such as correct inflation of the balloons with ~80 ml of water, decompression of the duodenum with a controlled intermittent negative pressure pump calibrated within the range of 60–80 mm Hg, free passage of PandiCath® channels, and correct connection of PandiCath® channels to the negative pressure equipment;
3. Duration of experimental treatment $\geq$6 h.

2.4. Conduct of the study

Patients enrolled in the study underwent assessments on Days 1, 2, 3, 4, 7, and 15 during hospitalization and during the final visit at discharge, unless the final visit occurred earlier. These visits were timed to allow for the assessment of inclusion and exclusion

criteria, evaluation of the presence or development of SIRS and MODS, assessment of AP severity, and evaluation of infectious or other complications. Additionally, a phone-based follow-up was conducted, whenever possible, > three months after patients' discharge to check for adverse events development and repeated hospitalizations for AP.

2.5. Outcome measures

In the study, a composite Primary Clinical Endpoint (PCE) was utilized, defined as the occurrence during the observation period of any individual events or combination of events, as outlined below:

1. *de-novo* MODS at or after 96 h post-hospitalization;
2. development of infectious complications;
3. formation of intestinal and pancreatic fistula;
4. bleeding from the vessels of pancreatobiliary region;
5. development of abdominal compartment syndrome;
6. development of obstructive jaundice;
7. death due to AP or its complications based on pathology report.

The events included in the PCE are aligned with the anticipated effects of the experimental treatment, particularly focusing on preventing the progression of AP and the development of associated complications.

2.6. Sample size

The study was conducted without prior estimation of the effect size, making it impossible to perform a credible power or sample size calculation. However, the protocol predefined a sample size of approximately 150–160 patients, and enrollment was halted upon reaching 154 patients.

2.7. Statistical analysis

Due to the study's exploratory nature, primary statistical analysis was performed using a modified intention-to-treat (mITT) principle. Results for categorical data, such as the PCE, were expressed as p-values from Z-test for proportions (Z-test) computed with online calculator (https://www.socscistatistics.com/tests/ztest/default2.aspx), relative risk (RRs) with p-value and 95 % CIs computed with online calculator (https://www.medcalc.org/calc/relative_risk.php), and Number-Needed-to-Treat (NNT) with 95 % CIs computed with online calculator (https://www.graphpad.com/quickcalcs/NNT2/). Continuous data were statistically compared using Student's t-test. A two-tailed $P < 0.05$ was considered statistically significant.

2.8. Analysis populations considered in the study

2.8.1. Primary analysis population

2.8.1.1. The modified intention-to-treat as randomized (mITT-r). mITT-r population included all randomized patients who met the study's enrollment criteria and did not meet withdrawal criteria. Patients who were randomized but later found to violate enrollment criteria or meet withdrawal criteria were excluded from the analysis to uphold data integrity. Allocation to study groups was determined through central randomization.

2.8.2. Additional analysis populations

2.8.2.1. The modified intention-to-treat as treated (mITT-t). mITT-t population included all patients meeting the criteria of the *mITT-r* population. Patients who received the correct experimental treatment with PandiCath® were categorized into experimental Group 1, while those who did not receive the correct experimental treatment were placed in SoC Group 2.

2.8.2.2. The full study as randomized (Full-r). Full-r population comprised all 154 patients enrolled in the study, including those who violated enrollment and/or met withdrawal criteria. Patients were assigned to study groups based on central randomization.

2.8.2.3. The full study as treated (Full-t). Full-t population included all enrolled patients. Patients who received the correct experimental treatment with PandiCath® were categorized into experimental Group 1, while all others were assigned to the SoC Group 2. The reasons for reassigning patients to Group 2 are detailed in Supplementary File: Table S4.

Table 1 presents a breakdown of the number of patients considered within the analysis populations of the study.

3. Results

3.1. Primary analysis population

Out of 154 patients enrolled in the study, 76 were randomized to Group 1 (PandiCath® + SoC) and 78 to Group 2 (SoC only). A total of 126 patients (81.82 % of those enrolled) were included in the *modified intention-to-treat as randomized (mITT-r)* analysis population, with 65 in Group 1 and 61 in Group 2 (see Table 1). The Supplementary File: Table S5 lists 28 patients (18.18 % of those enrolled) excluded from the mITT analysis populations accompanied by reasons for exclusion.

3.1.1. Patients' baseline demographics and clinical characteristics

A comparison of the study groups indicates a generally well-balanced distribution across all key demographic and clinical characteristics (Table 2A). Notably, Group 1 shows a slightly higher prevalence of patients presenting with SIRS and/or MODS upon admission, suggesting a potentially more severe disease profile within this cohort. A slightly higher proportion of Group 1 patients were also admitted to the intensive care unit (ICU), along with a slightly higher average volume of infusion received. Overall, patients in both study groups received comparable SoC treatment.

3.1.2. Primary outcome measures

The incidence of events contributing to the PCE is notably reduced by 15.66 % in Group 1 compared to Group 2 (13.85 % vs. 29.51 %) (Table 3A). This difference demonstrates a statistically significant effect, as confirmed by the Z-test ($P = 0.032$) and the Relative Risk (RR = 0.469, 95 % CI 0.228–0.964, $P = 0.039$). The Number Needed to Treat (NNT) value of 6.384 (95 % CI 3.349–68.167) indicates that approximately seven patients would need to be treated with PandiCath® in addition to SoC compared to SoC alone to prevent one adverse outcome described by the PCE.

3.1.3. Additional outcome measures

In addition to assessing the PCE, the study individually examined the events contributing to it, including the incidence of infection and other adverse events, the development of *de novo* MODS ≥96 h post-hospitalization, and mortality related to AP. Across all these parameters, a coherent trend was noted (Table 3A), indicating that the differences observed in the PCE are attributable to consistent changes in its constituent components.

Further comparison revealed a notable, although not statistically significant, trend toward reduction in the number of patients requiring surgical or non-surgical interventions (Table 3A) in the experimental Group 1 (Z-test $P = 0.195$; RR = 0.626, 95 % CI 0.305–1.285, $P = 0.203$). The number of interventions in Group 1

Table 1
Breakdown of the number of patients considered in the analysis populations of the study. The % indicate the proportion of the total enrolled in the study or randomized in a study group.

Patients randomized in the study			Total	Group 1	Group 2
			154	76	78
Patients considered according to treatment received			154	71	83
Primary analysis populaiton	*Modified intention-to-treat as randomized (mITT-r)* population	Included	126 (81.82 %)	65 (85.53 %)	61 (78.21 %)
		Excluded	28 (18.18 %)	11 (14.47 %)	17 (21.79 %)
Additional analysis populations	*Modified intention-to-treat as treated (mITT-t)* population	Included	126 (81.82 %)	61 (85.92 %)	65 (78.31 %)
		Excluded	28 (18.18 %)	10 (14.08 %)	18 (21.69 %)
	Full study as randomized (*Full-r*) population	Included	154 (100 %)	76 (100 %)	78 (100 %)
	Full study as treated (*Full-t*) population	Included	154 (100 %)	71 (100 %)	83 (100 %)

Table 2
Baseline demographic and clinical characteristics of analysis populations. *B – biliary pancreatitis, ** NB – non-biliary pancreatitis.

Modified intention-to-treat analysis populations		A					B				
		Modified intention-to-treat as randomized (mITT-r)					*Modified intention-to-treat as treated (mITT-t)*				
		Group 1		Group 2		P value	Group 1		Group 2		P value
		65		61			61		65		
Demographic and clinical characteristics	Gender	Male	Female	Male	Female	**0.920**	Male	Female	Male	Female	**0.787**
		63.08 %	36.92 %	63.93 %	75.41 %		62.30 %	37.70 %	64.62 %	35.38 %	
	Etiology	B*	NB**	B	NB	**0.684**	B	NB	B	NB	**0.660**
		21.54 %	78.46 %	24.59 %	75.41 %		21.31 %	78.69 %	24.62 %	75.38 %	
	Mean age (years)	45.82		46.00		**0.941**	44.38		47.34		**0.233**
	Mean BMI	28.12		29.33		**0.245**	28.36		29.04		**0.515**
Baseline severity of AP	MODS within the first 24hrs	27.69 %		21.31 %		**0.406**	27.87 %		21.54 %		**0.410**
	SIRS within the first 24hrs	78.69 %		66.67 %		**0.147**	77.97 %		67.86 %		**0.222**
Standard of Care (SoC) Treatment	Treated in ICU	76.92 %		70.49 %		**0.412**	78.69 %		69.23 %		**0.228**
	Liquid resuscitation	100 %		100 %		**N/A**	100 %		100 %		**N/A**
	Mean volume of infusion (L) – first 48hrs	6.95		6.48		**0.342**	7.02		6.45		**0.236**
	Mean volume of infusion (L) – second 48hrs	5.33		5.27		**0.903**	5.28		5.32		**0.940**
	Enteral feeding	100 %		100 %		**N/A**	100 %		100 %		**N/A**
	NSAIDs and spasmolytics	100 %		100 %		**N/A**	100 %		100 %		**N/A**
Full study analysis populations		**C**					**D**				
		Full study as randomized (Full-r)					***Full study as treated (Full-t)***				
		Group 1		**Group 2**		**P**	**Group 1**		**Group 2**		**P**
		76		**78**		**value**	**71**		**83**		**value**
Demographic and clinical characteristics	Gender	Male	Female	Male	Female	**0.836**	Male	Female	Male	Female	**0.931**
		63.16 %	36.84 %	61.54 %	38.46 %		61.97 %	38.03 %	62.65 %	37.35 %	
	Etiology	B	NB	B	NB	**0.778**	B	NB	B	NB	**0.569**
		23.68 %	76.32 %	25.64 %	74.36 %		22.54 %	77.46 %	26.51 %	73.49 %	
	Mean age (years)	45.86		47.03		**0.605**	44.28		48.30		**0.072**
	Mean BMI	28.23		28.78		**0.545**	28.45		28.57		**0.895**
Baseline severity of AP	MODS within the first 24hrs	31.58 %		24.36 %		**0.318**	30.99 %		25.30 %		**0.433**
	SIRS within the first 24hrs	76.39 %		64.29 %		**0.114**	76.81 %		64.38 %		**0.105**
Standard of Care (SoC) Treatment	Treated in ICU	80.26 %		67.95 %		**0.081**	81.69 %		67.47 %		**0.045**
	Liquid resuscitation	100 %		100 %		**N/A**	100 %		100 %		**N/A**
	Mean volume of infusion (L) – first 48hrs	7.24		6.16		**0.017**	7.30		6.18		**0.014**
	Mean volume of infusion (L) – second 48hrs	5.49		5.08		**0.300**	5.50		5.09		**0.313**
	Enteral feeding	98.68 %		100 %		**0.309**	98.59 %		100 %		**0.278**
	NSAIDs and spasmolytics	100 %		100 %		**N/A**	100 %		100 %		**N/A**

was 2.56 times lower than in the SoC Group 2 (16 vs. 41). This trend was even more pronounced for patients who suffered from infectious complications. Moreover, the complexity of interventions required by patients in Group 1 appears to have decreased (Table 4).

Finally, among patients treated in the ICU, Group 1 showed a reduction in the mean length of stay (LOS) in the ICU by 1.79 days (26.89 %) compared to Group 2 (4.88 days vs. 6.67 days). Group 1 had a 4.66-day (23.93 %) shorter total LOS compared to Group 2 (14.82 days vs. 19.48). Although not statistically significant ($P = 0.211$ for LOS in ICU; $P = 0.106$ for total LOS), potentially due to the study's limited size, these reductions could still significantly impact the costs and resources required for treating patients with AP.

3.2. Additional analysis populations

3.2.1 In the *modified intention-to-treat as treated* (*mITT-t*) population, out of the 126 patients included in the primary analysis population (*mITT-r*), 61 patients were considered as having received the correct experimental treatment with PandiCath® as defined in section 2.3. They were assigned to the experimental Group 1. Consequently, 65 patients, including four initially randomized to Group 1, were considered to have received standard of care (SoC) and were assigned to Group 2 (Table 1). Similar to the primary *mITT-r* population, the *mITT-t* population demonstrates a balanced distribution across key demographics and clinical characteristics (Table 2B). Group 1 displays a slightly higher prevalence

Table 3
Summary of statistical comparisons between study groups in analysis populations considered in the study. G1 − Group 1, G2 − Group 2.

Modified intention-to-treat analysis populations		A					B				
		Modified intention-to-treat as randomized (mITT-r)					*Modified intention-to-treat as treated (mITT-t)*				
		Group 1	Group 2	P value	RR	NNT	Group 1	Group 2	P value	RR	NNT
		65	61				61	65			
COMPOSITE PRIMARY CLINICAL ENDPOINT (PCE)		**9 (13.85 %)**	**18 (29.51 %)**	**0.032**	**0.469**	**6.385**	**7 (11.48 %)**	**20 (30.77 %)**	**0.008**	**0.373**	**5.183**
PCE constituent events	Infectious complications	5 (7.69 %)	12 (19.67 %)	0.049	0.391	8.347	3 (4.92 %)	14 (21.54 %)	0.006	0.228	6.017
	Infectious and/or non-infectious complications	5 (7.69 %)	13 (21.31 %)	0.029	0.361	7.343	3 (4.92 %)	15 (23.08 %)	0.004	0.213	5.507
	De novo MODS @≥96hrs post-admission	3 (4.62 %)	7 (11.48 %)	0.155	0.402	14.577	3 (4.92 %)	7 (10.77 %)	0.225	0.457	17.091
	AP related mortality	3 (4.62 %)	5 (8.20 %)	0.410	0.563	27.923	2 (3.28 %)	6 (9.23 %)	0.171	0.355	16.801
Interventions	Interventions for complications of AP	4 (6.15 %)	12 (19.67 %)	0.023	0.313	7.397	3 (4.92 %)	13 (20.00 %)	0.011	0.246	6.630
	All patients who underwent interventions	10 (15.38 %)	15 (24.59 %)	0.195	0.626	10.863	9 (14.75 %)	16 (24.62 %)	0.165	0.599	10.141
		Group 1	**Group 2**		**Ratio (G2/G1)**	**%Reduction (G1 vs. G2)**	**Group 1**	**Group 2**		**Ratio (G2/G1)**	**%Reduction (G1 vs. G2)**
	Number of interventions in patients with AP complications	8	37	N/A	4.63	78.38 %	7	38	N/A	5.43	81.58 %
	Total number of interventions in all patients	16	41	N/A	2.56	60.98 %	15	42	N/A	2.80	64.29 %
Length of Stay (LOS)		**Group 1**	**Group 2**	**P value**	**Difference (G2-G1)**	**%Reduction (G1 vs. G2)**	**Group 1**	**Group 2**	**P value**	**Difference (G2-G1)**	**%Reduction (G1 vs. G2)**
	Mean LOS in ICU for patients treated in ICU (days)	4.88	6.67	0.211	1.79	26.89 %	4.88	6.60	0.225	1.73	26.14 %
	Mean total LOS (days)	14.82	19.48	0.106	4.66	23.93 %	14.98	19.03	0.143	4.05	21.27 %
Full study analysis populations		**C**					**D**				
		Full study as randomized (Full-r)					***Full study as treated (Full-t)***				
		Group 1	**Group 2**	**P value**	**RR**	**NNT**	**Group 1**	**Group 2**	**P value**	**RR**	**NNT**
		76	**78**				**71**	**83**			
COMPOSITE PRIMARY CLINICAL ENDPOINT (PCE)		**13 (17.11 %)**	**22 (28.21)**	**0.100**	**0.606**	**9.009**	**11 (15.49 %)**	**24 (28.92 %)**	**0.048**	**0.536**	**7.450**
PCE constituent events	Infectious complications	8 (10.53 %)	15 (19.23 %)	0.130	0.547	11.488	6 (8.45 %)	17 (20.48 %)	0.037	0.413	8.312
	Infectious and/or non-infectious complications	8 (10.53 %)	16 (20.51 %)	0.088	0.513	10.014	6 (8.45 %)	18 (21.69 %)	0.024	0.390	7.555
	De novo MODS @≥96hrs post-admission	4 (5.26 %)	8 (10.26 %)	0.248	0.513	20.027	4 (5.63 %)	8 (9.64 %)	0.355	0.585	24.970
	AP related mortality	6 (7.89 %)	6 (7.69 %)	0.963	1.026	494.000	5 (7.04 %)	7 (8.43 %)	0.748	0.835	71.866
Interventions	Interventions for complications of AP	5 (6.58 %)	14 (17.95 %)	0.032	0.367	8.795	4 (5.63 %)	15 (18.07 %)	0.019	0.312	8.040
	All patients who underwent interventions	13 (17.11 %)	17 (21.79 %)	0.463	0.785	21.324	11 (15.49 %)	19 (22.89 %)	0.248	0.677	13.516
		Group 1	**Group 2**		**Ratio (G2/G1)**	**%Reduction (G1 vs. G2)**	**Group 1**	**Group 2**		**Ratio (G2/G1)**	**%Reduction (G1 vs. G2)**
	Number of interventions in patients with AP complications	9	39	N/A	4.33	76.92 %	8	40	N/A	5.00	80.00 %
	Total number of interventions in all patients	20	43	N/A	2.15	53.49 %	18	45	N/A	2.50	60.00 %
Length of Stay (LOS)		**Group 1**	**Group 2**	**P value**	**Difference (G2-G1)**	**%Reduction (G1 vs. G2)**	**Group 1**	**Group 2**	**P value**	**Difference (G2-G1)**	**%Reduction (G1 vs. G2)**
	Mean LOS in ICU for patients treated in ICU (days)	5.00	6.15	0.342	1.15	18.71 %	5.05	6.04	0.412	0.98	16.30 %
	Mean total LOS (days)	14.17	18.40	0.071	4.23	22.97 %	14.34	18.00	0.105	3.66	20.34 %

of SIRS and/or MODS, leading to more ICU admissions and higher infusion volumes within the first 48 h. Apart from these differences, both study groups received comparable SoC treatment.

As measured by PCE, a highly significant benefit associated with the experimental treatment is observed in the *mITT-t* population (Z-test P = 0.008; RR = 0.373, 95 % CI 0.170–0.819, P = 0.014). This finding is supported by the NNT value of 5.183 (95 % CI 3.024–18.134). Consistent trends were also observed across individual events constituting the PCE, the number of patients requiring surgical or non-surgical interventions, the number of interventions performed, LOS in the ICU, and total LOS (Table 3B).

3.2.2 In the *full study as randomized (Full-r)* population, all enrolled patients were included regardless of meeting inclusion, exclusion or withdrawal criteria and regardless of whether they received the correct experimental treatment. This approach fully adheres to the intention-to-treat principle but represents the most conservative analysis. The *Full-r* population exhibits no significant biases in the key clinical and demographic variables (Table 2C). Similar to other populations analyzed, Group 1 shows a trend towards a higher prevalence of patients with MODS and particularly SIRS upon admission. This observation aligns with the increased number of Group 1 patients admitted to the ICU and receiving a greater infusion volume within the first 48 h. All except one patient, with fulminant AP, received enteral feeding.

Table 4
Comparison of the interventions performed on patients in the analysis populations considered in the study.

Study analysis populations		A		B		C		D	
		Modified intention-to-treat as randomized (mITT-r)		*Modified intention-to-treat as treated (mITT-t)*		*Full study as randomized (Full-r)*		*Full study as treated (Full-t)*	
Study group		Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Number of patients who underwent intervention		10	15	9	16	13	17	11	19
Total number of interventions in all patients		16	41	15	42	20	43	18	45
Type of intervention	Non-diagnostic laparoscopic revision and drainage of peritoneum	1	5	1	5	1	5	1	5
	Non-diagnostic ultrasound-guided drainage of abdominal cavity	2	0	1	1	2	0	1	1
	Drainage of retroperitoneal space/peripancreatic abscess, ultrasound-guided	11	19	11	19	13	21	13	21
	Laparotomy, laparostomy, necrosectomy of the pancreas	2	16	2	16	2	16	2	16
	Drainage of biliary ducts/gallbladder	0	1	0	1	0	1	0	1
	ERCP	0	0	0	0	2	0	1	1

The effect of the experimental treatment in the *Full-r* population, expressed as PCE, is notable but does not reach the predefined statistical significance threshold for the study (Z-test P = 0.100, RR = 0.606, 95 % CI 0.330–1.115, P = 0.107; NNT = 9.009). However, it is consistent with other outcome measures except for AP-related mortality, where no difference is observed between the study groups (Table 3C). Interestingly, the approximately 23 % decrease in the overall LOS in Group 1 compared to Group 2 in this study population approaches the predefined statistical significance threshold (P = 0.071).

3.2.3. In the *Full study as treated (Full-t)* analysis population, 71 patients remained in the experimental Group 1, having received the correct experimental treatment. Five patients randomized to Group 1 were reassigned to SoC Group 2, consisting of 83 patients. In this population, patients' gender, BMI and AP etiology remained balanced between the groups (Table 2D). However, the age of patients turned out to be notably skewed towards younger individuals in Group 1 (P = 0.072). A higher prevalence of patients with MODS and particularly with SIRS upon admission is also evident in Group 1. This translates into a greater number of ICU admissions in Group 1 and a significantly higher volume of infusion administered within the first 48 h.

In the *Full-t* analysis population, the experimental treatment Group 1 demonstrates statistically significant improvement in the PCE (Z-test P = 0.048; RR = 0.536, 95 % CI 0.283–1.016, P = 0.055; NNT = 6.450, 95 % CI 3.801–185.338) and in the incidence of infectious and non-infectious complications. A reduction in the development of *de-novo* MODS, frequency and number of surgical procedures, AP-related mortality, and the LOS is also observed in Group 1 (Table 3D).

4. Discussion

The complex pathophysiology of AP underscores the importance of a comprehensive approach to treatment. Current clinical guidelines advocate for a multifaceted strategy emphasizing intensive therapy and early enteral feeding [29]. Combining these measures with the protection of the duodenum from gastric and intestinal contents, active decompression of the duodenum, and drainage of the gastric and intestinal contents may further improve treatment outcomes. Unlike other tools and clinical approaches, the PandiCath® catheter enables all these effects to be achieved simultaneously.

In this prospective randomized clinical study, we investigated whether the intervention with the PandiCath® device could translate into improved outcomes for patients with moderate or severe AP. Focusing on this patient population allowed us to target a significant medical need and increase the likelihood of detecting an effect in a smaller PoC study. We aimed to exclude patients with mild AP using parameters recommended in international guidelines, which could be evaluated within the study's enrollment timeframe. The high proportion of study participants admitted to the ICU and the considerable overall LOS (mean LOS in the primary analysis population being 14.82 days for Group 1 and 19.48 days for Group 2) indicate that this approach was effective. The study's enrollment timeframe aimed to initiate treatment with PandiCath® early, specifically within ≤48 h post-admission and ≤96 h post-symptom onset, aligning with routine clinical practice for AP patients. Additionally, the study aimed to evaluate the effectiveness of our developed treatment method in patients deemed more likely to benefit, while excluding those unsuitable for the treatment with PandiCath®. It also aimed to exclude cases where interpreting the intervention's effect might be challenging.

The composite Primary Clinical Endpoint (PCE) used as the primary outcome measure in the study encompasses the critical adverse events essential to AP development, which the experimental treatment aims to prevent. Additionally, we present data on the individual components of the PCE. While these components are interrelated and contribute to the overall PCE, they help in assessing the consistency of the treatment's effects. Lastly, we evaluated the impact on resource utilization for patient care, including incidence of surgical and non-surgical interventions, number of interventions, and LOS, offering further insights into the utility of the experimental intervention. The absence of information on long-term outcomes, patient-reported outcomes, and comprehensive economic evaluations is acknowledged as a potential shortcoming of the study and will be addressed in future research. However, we believe that focusing on early outcomes, such as infectious complications and MODS, is both relevant and justified given the PoC objectives of the study. These outcomes are critical drivers of morbidity and mortality in AP, making them key endpoints for the initial evaluation of the treatment's effectiveness.

Our comprehensive analyses of the treatment effects of PandiCath® across various populations accounted for patient characteristics and protocol adherence. Despite their interdependence, these analyses enhance the validity of our findings and provide valuable insights for future research. The primary analysis population, *modified intention-to-treat as randomized (mITT-r)*, comprised all eligible patients with study group allocations determined by central randomization. However, exclusions were made for cases unsuitable for experimental treatment or where evaluating treatment effectiveness was challenged by serious

Table 5
Change in the prevalence of MODS between admission and ≥96 h post-admission.

Analysis populations	*Modified intention-to-treat as randomized (mITT-r)*			*Modified intention-to-treat as treated (mITT-t)*			*Full study as randomized (Full-r)*			*Full study as treated (Full-t)*		
Study Groups	MODS at admission	MODS at ≥96 h post-admission	**% Change**	MODS at admission	MODS at ≥96 h post-admission	**% Change**	MODS at admission	MODS at ≥96 h post-admission	**% Change**	MODS at admission	MODS at ≥96 h post-admission	**% Change**
Group 1	27.69 %	18.46 %	**−9.23 %**	27.87 %	18.03 %	**−9.84 %**	31.58 %	22.37 %	**−9.21 %**	30.99 %	22.54 %	**−8.45 %**
Group 2	21.31 %	27.87 %	**6.56 %**	21.54 %	27.69 %	**6.15 %**	24.36 %	28.21 %	**3.85 %**	25.30 %	27.71 %	**2.41 %**

confounders. Exclusions were applied equally to both study groups, resulting in more patients from the SoC Group 2 being removed from *mITT* analyses than from Group 1. A statistically significant effect of PandiCath®-mediated treatment, as measured by the PCE, and a relatively low NNT (Table 3A) in this population suggest a potential clinical benefit of adding PandiCath® to the treatment regimen. However, the wide confidence interval of the NNT indicates uncertainty in the estimate, emphasizing the need for further research to confirm the findings. Analysis of the *modified intention-to-treat as treated (mITT-t)* population allows us to more precisely assess the efficacy of the experimental treatment in patients who received it as intended. Within this analysis population, the effects of PandiCath® appear more pronounced as indicated by highly significant PCE (Z-test P = 0.008, Table 3B).

We believe in a compelling rationale for deviating from the traditional intention-to-treat principle in a PoC study. However, it's essential to recognize that even with full transparency, this deviation may introduce a degree of subjectivity and potential biases, which could affect the study's validity and the conclusions drawn from it. To address this concern, we conducted *full study* analyses encompassing all enrolled patients, including those who were not originally intended for treatment with PandiCath®. When such an analysis is conducted with the actual treatment received by patients taken into account (*full study as treated* population), the PCE and the incidence of infectious complications continue to show statistically significant improvement in PandiCath® treated Group 1 (Table 3D). Interestingly, reassigning patients from Group 1 who received PandiCath® treatment later than protocol-mandated (>96 h post-symptom onset) to SoC Group 2, alongside those who did not receive the correct experimental treatment (as defined in section 2.3), results in a notable increase in statistical significance for the PCE (see Supplementary File: Table S6). This could suggest that earlier application of PandiCath® may be more likely to provide benefits.

Finally, we stress-tested the study by conducting the *full study as randomized (Full-r)* analysis, which fully adheres to the intention-to-treat principle but potentially represents the most conservative scenario by including all participants according to their randomized treatment assignment, regardless of actual treatment received or protocol adherence. Although neither the PCE nor other outcome measures reached the predefined statistical significance (Z-test P = 0.100 for the PCE), most displayed a consistent positive trend (Table 3C), aligning with observations in other analysis populations. No difference was observed between the groups in terms of AP-related mortality. Notably, among the six AP-related deaths in Group 1, one was associated with fulminant AP, where the benefit from PandiCath® would not have been expected. In three additional cases, patients presented with infectious complications at the time of enrollment and/or did not receive the appropriate experimental treatment with PandiCath®. This underscores the importance of considering individual patient circumstances and the nature of their conditions when interpreting study outcomes.

Before statistical analysis of the treatment effects, we evaluated the baseline characteristics of study groups to identify potential biases. Across all study populations, the key clinical and demographic variables appeared well-balanced, thus minimizing the likelihood of influencing the observed treatment effects and suggesting that the randomization process was objective.

Another important parameter evaluated was the baseline severity of AP across the study groups. Interestingly, in all populations analyzed, a higher prevalence of patients with MODS and SIRS was observed in Group 1 at enrollment, indicating a potentially more severe disease presentation in this group. This likely explains why Group 1 initially received more intensive treatment: more patients were admitted to the ICU and received a higher infusion volume in the first 48 h. However, despite more Group 1 patients being treated in the ICU, their LOS was shorter in all analysis populations (Table 3A–D). Additionally, while more patients in Group 1 had MODS at admission, after 96 h of treatment, the situation reversed (Table 5), due to fewer patients in this group developing *de novo* MODS. A similar trend was observed for SIRS.

Overall, patients in both study groups received comparable SoC treatment. The incidence of infectious complications and relatively low mortality in SoC Group 2 align with published observations [8,9,28], suggesting that patients received high-quality care. Furthermore, the multicenter nature of the study, conducted in regular city hospitals, supports the potential generalizability of the findings and ease of introducing PandiCath® into routine clinical practice.

The primary goal of the study was to evaluate the effectiveness of PandiCath® in combination with standard care for treating "non-mild" AP. While the study demonstrated potential effectiveness, particularly in reducing infectious complications, PandiCath® also showed a reassuring safety profile. Two significant device-related adverse events were observed: an allergic reaction to silicone and damage to the cardia due to self-removal of the catheter by a delirious patient. Both events were promptly managed and resulted in no serious or long-term harm to the patients. Additionally, nine out of the 74 patients (12 %) who had the PandiCath® device placed reported discomfort, which led to its removal in three cases due to patient complaints. These observations are consistent with previously published studies suggesting that approximately 10–30 % of patients with enteral catheters may report some degree of discomfort [30,31].

This study represents the first systematic attempt to evaluate the potential for treatment modalities conferred by PandiCath® to enhance outcomes for patients with AP. In this PoC study, compelling positive trends were observed. Specifically, the potential restoration by PandiCath® of certain physiological functions damaged in AP appears to positively influence the major adverse events contributing to the disease's morbidity and mortality, as well as the resources needed for patient treatment. The results of this study provide a basis for conducting properly powered and more rigorous clinical trials to assess the effectiveness and safety of PandiCath® and explore strategies for further enhancement. Investigating the mechanisms underlying the benefits of PandiCath®-enabled treatment could optimize its therapeutic use, and this avenue should be actively pursued.

Authorship statement

This manuscript has been read and approved by all authors; the established authorship requirements have been met.

Declaration of competing interest

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Appendix A. Supplementary data

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