CONTINUOUS ROPIVACAINE INFUSION VIA EPIDURAL CATHETER IMPROVING GASTROINTESTINAL DYSFUNCION IN ACUTE PANCREATITIS: A PRELIMINARY STUDY

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This preliminary study aimed to evaluate the effectiveness of continuous infusion of ropivacaine via an epidural catheter in improving gastrointestinal dysfunction in patients with severe or predicted severe pancreatitis. Of 27 patients, 21(77.8%) were male, and the mean age was 49 ± 10.9 years. Fourteen patients were in the epidural analgesia (EA) group and thirteen patients were in the non-epidural analgesia (NEA) group. There was a trend of improvement of GIF score in the EA group. The mean of GIF score day 1, day 2 and day 3 in the epidural group was significantly less than NEA group (2.19 ± 0.65 vs 2.77 ± 0.76, p-value = 0.043). In a population of critical care unit adults with severe acute pancreatitis or predicted severe acute pancreatitis, this preliminary study showed that continuous infusion of ropivacaine via an epidural catheter may have some benefits in gastrointestinal function. Further comparative investigations with large study populations and multicenter data are necessary.

Keywords: Acute pancreatitis, pain control, organ failure, gastrointestinal failure, epidural anesthesia.

I. INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas, characterized by severe abdominal pain. The two major consequences of AP are pain and progression to severe acute pancreatitis (SAP) with organ failure. Managing this pain effectively is crucial.[1] Moreover, 20% of AP patients will develop a severe form with a mortality rate of 13 to 35%[2]. Multiple organ failure is a serious complication of SAP with a high mortality rate, such as respiratory failure, acute kidney injury and especially gastrointestinal failure. Additionally, gastrointestinal failure is an important organ failure in patients with AP and is an independent predictor of mortality.[3] SAP has the two major clinical phases: the first period is characterized by systemic inflammatory response syndrome (SIRS) and the second period is marked by infectious complications, which accounts for most late deaths of patients with SAP.[1] Sepsis associated with secondary infection of pancreatic necrosis is mainly caused by Gram-negative enteric organisms. This phenomenon suggests a gastrointestinal origin and dysfunction of the gut barrier during the development of sepsis and multiple organ dysfunction syndrome (MODS) in patients with SAP.[1]

Recently, epidural analgesia (EA) is used to control pain in patients with AP. In some systematic reviews and meta-analysis, EA has been recognized not only as a safe and effective method to control pain but also as a potential therapy to reduce organ dysfunction by improving organ perfusion and improve the prognosis for patients.[1,4,5] While some initial

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Received: 15/05/2024
Accepted: 08/07/2024

studies have evaluated its effectiveness in improving organ dysfunction, no research has yet assessed its impact on gastrointestinal dysfunction in patients with AP.

Therefore, we conducted a study to evaluate the effectiveness of continuous infusion of 0.1% ropivacaine via an epidural catheter in improving gastrointestinal dysfunction in patients with severe or predicted severe pancreatitis.

II. METHODS

This is a single-center interventional open-label randomized controlled trial. The study protocol was approved by The Hanoi Medical University Institutional Ethical Review Board (HMU IRB) (Ref: 689/GCN-HDDDNCYSH-DHYHN, dated August 01, 2023).

1. Study population

The study was conducted at Bach Mai Hospital in Hanoi, from August 2023 and February 2024. The inclusion and exclusion criteria were as follows:

2. Participant inclusion criteria

- Aged ≥ 18 years.

- Diagnosis of acute pancreatitis required two of the following three features, as per the revised Atlanta definition:[6] abdominal pain consistent with acute pancreatitis, serum lipase activity at least three times greater than the upper limit of normal, and characteristic findings of acute pancreatitis on contrast-enhanced computed tomography.

- Onset ≤ 72 hours.

- Pain moderate or severe with visual analog pain scale (VAS) ≥ 4 in consciousness patients or behavioral pain scale (BPS) ≥ 7 in unconsciousness patients.

- Classification is severe acute pancreatitis (modified Marshall score ≥ 2 on admission) or predicted severe (at least one of criteria:

(1) Ranson's Criteria ≥ 2 points;

(2) CRP level > 100 mg/L;

(3) Pancreatic necrosis on contrast-enhanced computed tomography.

3. Participant exclusion criteria

Patients fulfilling one or more of the following criteria were not included:

- Prothrombin index < 60%, platelet count < 75 G/L, curative anticoagulant therapy with heparin interrupted for less than 8 hours.

- Local infection in thoracic spine area.

- Failed procedure.

- Anaphylaxis history with ropivacaine, lidocaine, ropivacaine.

- Local anesthetic systemic toxicity history.

- Pregnancy.

4. Methods

Patients were randomized to one of two groups (intervention group (EA group) and control group (NEA group)). Block randomization was done through computer-generated table in groups of 4,6,8 patients.

In the interventional group, thoracic epidural analgesia was performed using ropivacaine 0,1% with a continuous infusion rate of 5 to 10 mL/h, through continuous infusion via thoracic epidural catheter. It was placed in an intervertebral space between the 8th and the 11th thoracic vertebra. In both groups, conventional analgesia was included in enteral and/or parenteral administration according to the WHO analgesics ladder (including paracetamol, nefopam, tramadol, and opioids). The route, dose, and frequency of analgesic administrations was based on clinical doctors of the Center for Critical Care Medicine – Bach Mai Hospital.

Analgesia goals were the same in the two groups, with regular evaluation of pain every 4 hours and during routine daily nursing care. The

other treatments were managed by attending physicians, which include fluid resuscitation, correction of electrolyte balance and acid-base balance, etiological treatment, early enteral nutrition, and early mobilization, when possible, diagnosis and treatment of complications. The intervention group received a continuous epidural infusion of ropivacaine 0.1% during the first 3 - 5 days at the Center for Critical Care Medicine – Bach Mai Hospital (CCCM-BMH). All other treatments were usual practice. Trained anaesthetists were recruited to perform in the study. The study was designed to be inclusive of 5 visits (daily in CCCM-BMH). The continuous epidural infusion of the ropivacaine technique can be performed in the CCCM-BMH. Adherence to trial protocol was assessed by the number of days the patient received intervention. These data were categorized as incomplete (< 3 days) and complete (at least 3 days).

Outcomes

The primary endpoint was the mean of GIF score on the first three days when patients were at the Center for Critical Care Medicine – Bach Mai Hospital. Patients were evaluated for GIF scores (table below) once a day, then the average GIF score from 3 assessments was calculated.

GIF score[7]	
Points	Clinical symptomatology
0	Normal gastrointestinal function
1	Enteral feeding < 50% of calculated needs or no feeding 3 days after abdominal surgery
2	Food intolerance (enteral feeding not applicable due to high gastric aspirate volume, vomiting, bowel distension, or severe diarrhea) or IAH
3	Food intolerance and IAH
4	Abdominal compartment syndrome

GIF: Gastrointestinal failure; IAH: intra-abdominal hypertension.

The secondary endpoint: the number of days in CCCM, in-hospital mortality.

Sample size

There is no published trial regarding the effect of epidural analgesia on pancreatitis including gastrointestinal failure and GIF score. This was a preliminary study that included 15 patients in each group.

5. Statistical analysis

All statistical analyses were performed using JASP software (University of Amsterdam).

Qualitative and continuous variables were described as percentages and medians (with interquartile ranges [IQRs]). Quantitative variables were compared using the Mann–Whitney *U* test or Wilcoxon signed rank test. *P*-values < 0.05 were considered significant.

III. RESULTS

Our study included 27 patients with acute pancreatitis, who were treated at the Center for Critical Care Medicine - Bach Mai Hospital from August 2023 to February 2024. The mean of the number of days in CCCM was 8.3 ± 3.3 days. Patient characteristics were described in the table below.

Table 1. Patient characteristics at time of ICU admission

Characteristic	Total	NEA group (N = 13)	EA group (N = 14)	p-value
Age (years)	49 ± 10.9; 31-75	51.7 ± 9.8; 38-67	46.5 ± 11.5; 31-75	0.22
Gender (male; %)	21; 77.8%	10; 76.9%	11; 78.6%	0.92
BPS	6.3 ± 2.3; 3-12	6.2 ± 2.4; 3-10	6.4 ± 2.3; 3-12	0.89
Glasgow coma scale	15	15	15	
MAP (mmHg)	92.1 ± 12.1; 63-113	93.1 ± 12.5; 63-108	91.3 ± 12.2; 73-112	0.71
P/F ratio	303 ± 110; 143-535	286 ± 123; 143-535	320 ± 97; 166-480	0.45
Serum creatinine (mg/dL)	98.5 ± 62.5; 13-298	114.7 ± 56.3; 43-225	83.4 ± 66.2; 13-298	0.20
Bilirubin (µmol/L)	18.7 ± 10.0; 6.6-39.8	20.6 ± 10.7; 7-39.8	17.0 ± 9.3; 6.6-37.8	0.35
PLT (/mm3)	175 ± 76; 72-369	155.5 ± 63; 79-299	193 ± 84; 72-369	0.21
Heart rate (bpm)	121 ± 21; 68-150	120 ± 24; 68-150	122 ± 20; 88-150	0.86
Respiratory rate (/min)	29.8 ± 7.3; 18-45	31.0 ± 8.2; 18-45	28.7 ± 6.4; 20-40	0.43
Temperature (^oC)	37.3 ± 0.8; 36.5-39.0	37.3 ± 0.79; 36.5-39	37.3 ± 0.74; 36.5-39	0.88
WBCs (/mm^3)	10.3 ± 4.6; 3.7-22.7	10.6 ± 4.7; 3.7-18.1	10.1 ± 4.7; 4.8-22.7	0.77
Arterial pH	7.32 ± 0.08; 7.12-7.49	7.32 ± 0.08; 7.18-7.45	7.33 ± 0.09; 7.12-7.49	0.73
Hematocrit (%)	40.2 ± 8.3; 26-55	40.5 ± 7.4; 27-55	39.9 ± 9.4; 26-55	0.87
Serum lactate (mmol/L)	3.23 ± 1.96; 0.9-7.5	3.5 ± 2.1; 1.1-7.5	2.9 ± 1.8; 0.9-6.7	0.47
Serum potassium (mmol/L)	3.66 ± 0.56; 2.7-5.2	3.66 ± 0.69; 2.7-5.2	3.66 ± 0.44; 3.0-4.8	0.99
Serum sodium (mmol/L)	132.5 ± 5.7; 118-142	133.2 ± 4.7; 125-142	131.8 ± 6.6; 118-140	0.56

Characteristic	Total	NEA group (N = 13)	EA group (N = 14)	p-value
GIF at admission	3.1 ± 0.73; 1-4	3.2 ± 0.55; 2-4	3.0 ± 0.88; 1-4	0.59
IAP at admission (cmH_2O)	22.4 ± 6.3; 11-37	22.9 ± 6.0; 15-37	21.9 ± 6.7; 11-32	0.67

MAP: mean arterial pressure; EA: Epidural aesthesia; NEA: non – epidural aesthesia; BPS: Behavioral pain scale; P/F: PaO_2/FiO_2 ratio; PLT: platelets; WBCs: white blood cells; GIF: gastrointestinal failure score; IAP: intra-abdominal pressure.
Data included mean ± SD;Min-Max.

In the study sample, patients exhibited similarities in terms of pain levels, organ function, and results from basic tests at time of CCCM admission.

Table 2. Gastrointestinal failure score

	EA group (N=14)	NEA group (N=13)	p-value
GIF score day 1	3.0 ± 0.88;1-4	3.15 ± 0.56;2-4	0.59
GIF score day 2	2.29 ± 0.83;1-4	2.92 ± 0.86;2-4	0.06
GIF score day 3	1.29 ± 0.99;0-3	2.23 ± 1.30;0-4	0.043
Mean GIF score	2.19 ± 0.65	2.77 ± 0.76	**0.043**

Secondary outcome

Table 3. The number of days in ICU and mortality rate

	EA group (N=14)	NEA group (N=13)	p-value
The number of days in CCCM	7.5 ± 2.8	9.1 ± 3.7	0.25
In-hospital mortality rate	0	0	

IV. DISCUSSION

Acute pancreatitis remained as a disease with high mortality, especially in severe acute pancreatitis and predicted severe acute pancreatitis and there are no disease-modifying therapies. This was a pilot study that evaluated the effect of epidural analgesia on gastrointestinal dysfunction in severe acute pancreatitis and predicted severe acute pancreatitis.

Severe and predicted severe acute pancreatitis patients receiving continuous infusion of 0.1% ropivacaine via an epidural catheter combined with usual care had lower GIF scores on days 2, 3 and mean GIF score than those receiving usual care alone. Moreover, GIF score decreased faster in the intervention group than in the control group. On

the first day, the GIF score in both groups was equivalent. On the second day, the GIF score in the intervention group decreased faster than in the control group. On the third day, the GIF score in the intervention group decreased significantly faster than in the control group, and the difference in GIF scores between the intervention and control groups was statistically significant. This change is clinically meaningful. It showed that the epidural analgesia group experienced a marked improvement in digestive function. The reason might be that epidural analgesia made an improvement in pancreas perfusion and other organs perfusion in the abdominal cavity.

There was paucity of evidence of epidural analgesia can improve organs failure.[4,8] The EPIPAN trial did not show the benefit of epidural analgesia in patients with acute pancreatitis and low requirement for intubation.[4] The primary outcome of EPIPAN trial was the number of ventilator-free days from randomization until day 30 and had no gastrointestinal failure assessment. Respiratory failure was not only a consequence of acute pancreatitis but might be the result of an extremely aggressive fluid resuscitation in the first phase of acute pancreatitis treatment. In a study from Asha Tyagi et al, there was an insignificant clinical trend towards better organ functions[8]without contraindication to TEB were randomized to receive (group TE. The sequential organ failure assessment (SOFA) score was the method of choice for quantifying organ functions in that study. But the sample size was low. In our study, there was not a mortality reduction and the number of days in CCCM. It might be because of a small sample size of our study.

Our study had some limitations. First, the small sample was not very representative. Future studies should be conducted with larger sample sizes in acute pancreatitis population. Second, as mentioned above, there was a need for more specific tools to evaluate gastrointestinal failure. For instance, it was necessary to evaluate gastrointestinal imaging and some special biochemical tests. Therefore, further evaluations are needed in future studies.

In summary, in a population of adults critically ill patients with severe acute pancreatitis or predicted severe acute pancreatitis, this preliminary study showed that continuous infusion of ropivacaine via an epidural catheter may have some benefits in gastrointestinal function. Our findings support the use of epidural analgesia in the early phase of acute pancreatitis. Further comparative investigations with large study populations and multicenter data are necessary.

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