南昌大学第一附属医院
THE FIRST AFFILIATED HOSPITAL OF NANCHANG UNIVERSITY

Neostigmine Treatment of Acute Pancreatitis Combined With Intra-abdominal Hypertension： A prospective, randomized, controlled trial

NCT02543658

Approval Number: （2015）NO.011

2015/6/2

Board Name: Ethics Committee of the Frist Affiliated Hospital of Nanchang University
Phone: 0791-88691867 Ext: yfykjk@126.com

Introduction

Acute pancreatitis (AP) is a common disease of digestive system, severe acute pancreatitis(SAP) with persistent organ failure is associated with an increased risk of death[1]. Intra-abdominal hypertension (IAH) is defined as persistent increase of intra-abdominal pressure (IAP) > 12 mm, according to the World Society for Abdominal Compartment Syndrome (WSACS)[2] . IAH was considered as an early factor in the pathogenesis of SAP[3]. In a prospective study, IAH was diagnosed in 17% of patients with AP(most on admission), with a mortality rate of 37%[4]. This inflammation starts a cascade of pancreatic and visceral edema, acute peripancreatic fluid collections, capillary leakage causing ascites, paralytic ileus, and gastric dilatation leading to an elevated IAP[5].

When the intra-abdominal pressure (IAP) continues to rise above 20 mmHg, it may lead to new organ failure or acute deterioration of existing organ failure, this is called abdominal compartment syndrome (ACS) [2]. ACS develops in AP is associated with a mortality rate of 49%[5]. Although surgical decompression results in prompt recovery from ACS, it has substantial morbidity associated with the management and complications of open abdomen. This includes infected pancreatic necrosis, intra-abdominal bleeding, development of post-operative fistulas and hernias[5].

Currently, non-operative strategies to counter IAH in AP should be considered initially, include sedation and analgesia, neuromuscular blockade, body positioning, nasogastric/ colonic decompression, promotility agents, diuretics and continuous renal replacement therapies, fluid resuscitation strategies, percutaneous catheter drainage (PCD)[2, 3]. Neostigmine is an anti-cholinesterase drugs, can enhance intestinal peristalsis, promote flatus defecation. Studies have reported that treatment with neostigmine may be effective at inducing colonic decompression among those with colonic pseudo-obstruction [6].WSACS suggest that neostigmine be used for the treatment of established colonic ileus not responding to other simple measures and associated with IAH[2]. However, no data exist on the effects of pharmacologic promotility therapy on IAP or outcomes among those with IAH/ACS[2]. The aim of this study was to evaluate the efficacy of neostigmine on reducing IAP in AP patients with IAH.

Methods

Design: This is a single-center, two-armed, parallel group, superiority, randomized controlled clinical trial. AP patients with IAH (IAP ≥ 12 mmHg) received conservative treatment (gastrointestinal decompression, percutaneous catheter drainage of ascites and etc.), if IAP is still ≥ 12 mmHg after 24 hours were randomised into interventional group (intramuscular neostigmine bid to qid for 7 days) and conventional group (continuing conservative treatment).

Trial organization, committees and boards

The designer of the trial is the first affiliated hospital of Nanchang University, China（http://www.cdyfy.com/）. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University on the April 20th, 2015 (approval No. 2015 [003]). The study is performed in accordance with the declaration of Helsinki. An independent data safety and monitoring committee (DSMC) will evaluate the progress of the trial and examine the safety variables at regular intervals. All physicians involved in the study will repetitively be asked to report any potential adverse events. All possible adverse events will be listed and discussed with the DSMS, and reported to the Ethics Committee of the First Affiliated Hospital of Nanchang University. Informed consent will be obtained from each participating patient in oral and written form prior to randomisation. If a patient is unable to sign by himself/herself, his / her family member will be authorized to sign it.

Study population

AP patients with IAH (IAP ≥ 12 mmHg) with IAH assessed for eligibility, if IAP is still ≥ 12 mmHg after received conservative treatment (gastrointestinal decompression, percutaneous catheter drainage of ascites and etc.) for 24 hours, participants will be signed informed consent and randomized into two groups if they meet all the inclusion criteria and no exclusion criteria.

Inclusion criteria

The inclusion criteria are:

1) Age 18-70 year ;

2) The diagnosis of acute pancreatitis according to the revised Atlanta classification: (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging;

3) IAH is defined is defined by the World Society of Abdominal Compartment Syndrome (WSACS): ≥ 12 mmHg

4) After 24 hours of conventional treatment such as gastrointestinal decompression or percutaneous drainage of ascites, the IAP was still ≥ 12 mmHg;

5) The onset time of acute pancreatitis was within 2 weeks.

6) Signed the informed consent.

Exclusion criteria

The exclusion criteria are:

1) History of laparotomy;

(2) Mechanical ileus or abdominal hemorrhage were considered clinically;

(3) Those who have contraindications to neostigmine: patients with angina, myocardial infarction, ventricular tachycardia, bradycardia, acute circulatory failure, epilepsy, bronchial asthma, mechanical intestinal obstruction, urinary tract infarction, hyperthyroidism, serious arrhythmia, bladder operation, intestinal fistula, etc;

(4) Allergic to neostigmine;

(5) Pregnant or lactating patients.

Sample size

This study is a superior efficacy trial, hypothesizing a reduction in the primary endpoint in favour of the neostigmine treatment. The sample size was calculated based on our previous clinical observation data, that the decrease rate of IAP was 30% after treatment with neostigmine for 24 hours, and 5% in conventional treatment at 24 hours. Therefore, an absolute reduction in primary endpoint of 25% is anticipated. With a two-sided confidence level of 95% and 80%,With a 2-sided 5% alpha, power of 80%, and 10% loss to follow-up, the sample size was set at 40 cases per group, a total of 80 cases

Diagnosis of IAH and time of randomization

We measure IAP every 6 h for all AP patients in the pancreatic intensive care unit. IAP is measured indirectly (using intravesicular pressure as measured through a bladder catheter) 2 . Based on IAP, IAH is graded as follows; Grade 1 wherein IAP ranges between 12 and 15 mmHg, Grade 2 wherein IAP ranges between 16 and 20 mmHg, Grade 3 with IAP between 21 and 25 and Grade 4 with IAP >25 mmHg. AP patients with IAH (IAP $\geq$ 12 mmHg) with IAH will assessed for eligibility, if patients meeting all inclusion criteria and no exclusion criteria can be randomized after signed informed consent.

Randomization method

A randomization list is generated by a computer program, and the randomization information will sealed in envelopes. After randomization, the data will be record case report form by the Clinical esearch coordinator. Participants will be allocated to interventional group and conventional group and in a 1: 1 ratio. Blinding: participants will be blinded until the allocation to prevent patients being assigned to interventional group and conventional group. From assignment to intervention, blinding cannot be provided considering the study characteristics.

Study duration

The planned starting date of the study is September 2015, and the planned finishing date is December 2017.

Primary Endpoints

The primary outcome measure was decreased rate of IAP after randomization. We will measure the IAP in 3 hours after randomization, and then once every 6 hours for 7 consecutive days. Finally, we compared the IAP at each time point after

randomization with that before randomization.

Secondary endpoints

The following secondary endpoints will be analysed: (1) increase in Stool Volume at 1-7 days After randomization; (2) new-onset ACS; (3) new-onset organ failure, organ function will be monitored daily in all patients by the modified Marshall scoring system. (4) timing of enteral nutrition; (5) deterioration of IAH; (6) the Security of Neostigmine; (7) days in Hospital; (8) days in ICU and (9) medical expenses, which include all medications, services, salaries of healthcare professionals, equipment and day care costs.

Intervention

In this study, intramuscular injection of neostigmine will be the interventions. Patients will be randomized into interventional group and conventional group. The intervention will be started after randomized in all cases.

In interventional group, patients will undergo intramuscular injection of neostigmine on the basis of conventional conservative treatment. The initial dose of neostigmine was 1mg, ntramuscular injection(IM) once every 12 hours. If there is no defecation after 12 hours, the dose is increased to 1mg IM once every 8 hours; if there is no defecation after 24 hours, the dose is increased to 1mg IM once every 6 hours. If the abdominal pressure drops below 12mmHg, neostigmine will be stopped, otherwise it will be used continuously for 7 days.

The conventional group and interventional group will receive conservative treatment as follows: gastrointestinal decompression with nasogastric tube and rectal tub; 50ml paraffin oil will injection into gastric cavity through gastric tube , once every 8 hours; lycerin enema bid to tid to promotes defecation; patients with ascites undergo percutaneous puncture drainage.

Timing for surgical decompression

There will be a multidisciplinary discussion among surgeons, interventional doctors, gastroenterologists, and critical care physicians to decide whether to operate, when non-operative strategies to counter IAH fails. In general, surgical decompression is justified at IAP greater than 25 mmHg and presence of progressive organ dysfunction and fulminant ACS[3].

General treatment regimen

After initial fluid resuscitation, removal of excess fluid by using intravenous albumin and diuretics, or renal replacement therapy if needed. Sedation and analgesia be optimized to avoid agitation and respirator dyssynchrony[2]. Patients with an IAP <15 mmHg will receive enteral nutrition through the nasal jejunal tube, the rate was initiated at 20 mL/h and increased gradually by 15 mL every 8 h to the goal rate, depending on the patient's tolerance[7]. EN will be temporarily stopped when the IAP > 15 mmHg, and parenteral nutrition (PN) will be initiated. All patients with

infected pancreatic necrosis(IPN) will receive broad-spectrum antibiotic therapy according to institutional protocols. Antibiotic treatment is tailored based on blood cultures and culture from material collected during drainage. If patients with IPN and an indication for intervention will underwent either initial endoscopic transluminal drainage or PCD followed, if necessary, by endoscopic or surgical necrosectomy.

Data collection

During hospitalization, clinical data on baseline characteristics and outcomes were collected using standardized case record forms (CRF). An independent monitor checks the source data and CRF data after all patients completed the clinical study.

Follow up

All patients were followed up for 1, 3 and 6 months after discharge. During these visits, all patients will receive routine CECT, exocrine and endocrine pancreatic function tests.

Statistical analysis

Demographic and baseline characteristics will be analysed using descriptive analysis. After the last patient has completed the follow-up, there will be a blind assessment of all primary and secondary endpoints. Both intention to treat analysis(all patients are analysed according to their initially assigned study arm regardless of adherence to study protocol) and per protocol analysis(enrolled patients who finished the study conforming to the requirements of the study protocol) will be performed. Primary and secondary endpoints were compared between treatment groups. Descriptive statistics includes mean, standard deviation, median, quartiles and relative frequency. T test will be performed for continuous variable in the case of normal distribution, and Kruskal-Wallis test in the absence of a normal distribution. The X^2 test will be performed for categorical variables, and relative risk for dichotomous variables. Two tailed $P < 0.05$ was considered statistically significant.

References.

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.

2. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013;39:1190-206.

3. Trikudanathan G, Vege SS. Current concepts of the role of abdominal compartment syndrome in acute pancreatitis - an opportunity or merely an epiphenomenon. Pancreatology 2014;14:238-43.

4. Aitken EL, Gough V, Jones A, et al. Observational study of intra-abdominal pressure monitoring in acute pancreatitis. Surgery 2014;155:910-8.
5. van Brunschot S, Schut AJ, Bouwense SA, et al. Abdominal compartment syndrome in acute pancreatitis: a systematic review. Pancreas 2014;43:665-74.
6. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 1999;341:137-41.
7. Sun JK, Li WQ, Ke L, et al. Early enteral nutrition prevents intra-abdominal hypertension and reduces the severity of severe acute pancreatitis compared with delayed enteral nutrition: a prospective pilot study. World J Surg 2013;37:2053-60.