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Sham Feeding with Chewing Gum in Early Stage of Acute Pancreatitis: A Randomized Clinical Trial

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Background: The correlation between sham feeding and acute pancreatitis (AP) has only been examined in limited studies. We aimed to investigate the efficacy and safety of sham feeding in the early stage of AP.

Material/Methods: A randomized controlled clinical trial was performed. Equal groups of AP patients were recruited. Patients in the sham feeding group received chewing gum 4 times a day after admission. All patients in the trial received standard treatment consistent with the guidelines for AP. The primary outcomes were mortality, length of stay (LOS), and medical expenses. Secondary outcomes were the incidence of complications and other adverse events, return of gastrointestinal function, the details of enteral nutrition and intra-abdominal pressure.

Results: From May 2014 to December 2015, a total of 204 patients were recruited. The LOS and hospital costs in the sham feeding group were reduced, although mortality was equivalent between groups. The return of gastrointestinal function occurred earlier in the sham feeding group, with no complications related to gum chewing.

Conclusions: Sham feeding with chewing gum is safe and efficacious in the early stage of AP.

MeSH Keywords: Chewing Gum • Pancreatitis • Randomized Controlled Trial

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Background

Acute pancreatitis (AP) is a common acute abdominal disease that may be caused by a variety of etiologies, such as gallstones, high-fat diets, and immune factors. Mild AP can be cured by symptomatic treatment alone [1]. However, approximately 20% of patients with AP may develop severe acute pancreatitis (SAP), which is associated with rapid progression, frequent complications, and exceptionally high mortality [2].

Numerous studies have shown that the intestinal function disorder occurring in the early stage of AP results in decreased intestinal motility [3]. This intestinal function disorder is thought to be related to the systemic inflammatory response, intestinal ischaemia-reperfusion injury, and stimulation of local fluid collection in the retroperitoneal space and abdominal cavity [4]. Decreased intestinal motility makes AP progress [5]. Decreased intestinal motility worsens gastrointestinal bloating, increases intra-abdominal pressure (IAP), and probably induces abdominal compartment syndrome (ACS), a fatal complication of AP [6]. It can also lead to the alteration of intestinal flora, which dramatically increases the risk of enterogenous infection [7]. In addition, intestinal motility is closely associated with the implementation of enteral nutrition (EN) [8]. Decreased intestinal motility may lead to failed or delayed EN. In fact, EN has been confirmed as one of the most important treatments for AP and is closely associated with the prognosis [9]. Thus, the clinical study of AP has focused on how to reduce the incidence of intestinal motility disorders and promote their recovery.

In the past decade, the important role of enhanced recovery after surgery (ERAS) has become widely recognized [10]. The underlying goals of this approach are to reduce morbidity, enhance the rate of recovery, and shorten the postoperative length of stay (LOS) [11]. Sham feeding is a method used in ERAS for promoting the recovery of gastrointestinal motility [12,13]. Research has shown that sham feeding can activate the cephalic-vagal reflex and thus promote gastrointestinal motility by humoral and nervous stimulation [14,15]. At present, sham feeding has been successfully applied in postoperative management following several surgeries [16]. Sham feeding can be also be effective after colon [17] and breast surgeries [18]. However, there is limited evidence regarding whether sham feeding also plays a role in the treatment of AP. Therefore, this prospective, randomized, controlled trial was performed to investigate the efficacy and safety of gum chewing, a type of sham feeding, in the early treatment of AP.

Material and Methods

Research design

This was a single-center, randomized, controlled trial registered in the Chinese Clinical Trail Registry (ChiCTR-OCH-13003427). All of the pancreatitis patients admitted to Chengdu Military General Hospital were screened for trial eligibility. The patients enrolled in this study were randomly assigned into either the sham-chewing group or the control group. All of the patients enrolled or their legal representatives provided written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Chengdu Military General Hospital (LKPZ201413). All authors had access to the study data and approved the final manuscript.

Selection criteria

The following inclusion criteria were used: (1) AP was diagnosed consistent with the revised Atlanta classification [19] and (2) ages between 18 and 70 years. The exclusion criteria were as follows: (1) AP subsequent to a second disease, endoscopic retrograde cholangiopancreatography (ERCP), or suspected malignancy of the pancreas or biliary tree, (2) medical history of immune deficiency and abdominal operation or diagnosis of pancreatitis first made during surgery, or (3) inability to provide informed consent.

Randomization and blinding

The randomization was performed utilizing a computer-generated random allocation sequence. Numbered opaque envelopes were used for concealment, kept at a central location, and opened sequentially. Randomization, opening of envelopes, and allocation were all performed by a statistician who was not involved with the study.

However, it was difficult to keep the sham feeding completely blind to the patients, ward nurses, and the research assistant without a suitable placebo-control. All other clinicians and investigators were blinded.

Intervention and treatment

Patients allocated to the sham feeding group were instructed to chew gum for 15 min 4 times a day (usually at 8: 00, 12: 00, 16: 00, and 20: 00). The other treatments were performed consistent with the guidelines for AP [20,21]. These treatments mainly included early fluid resuscitation, targeted antibiotic therapy, early EN, and the management of local and systemic complications. Further step-up interventions, consisting of percutaneous catheter drainage, minimally invasive debridement,

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and open laparotomy, were utilized for those patients who developed infected peri-pancreatic necrosis [22,23]. The patients in the control group received the same treatments except for chewing gum.

Primary and secondary outcomes

The primary outcome of this study was to determine the effectiveness and safety of sham feeding in the treatment of AP. The effectiveness was measured by the clinical outcomes. The safety was measured by the incidence of complications and other adverse events.

The following outcome variables were analyzed as secondary outcomes: return of gastrointestinal function (time to first flatus and time to passage of feces), the details of EN (time to full tolerance of oral diet and time to achieve the energy target), IAP, hospitalization days, and medical expenses.

Data collection

Data were collected by an independent investigator not involved in the clinical management. Baseline characteristics (including age, sex, and etiology), laboratory test results, and several clinical scores were recorded at admission. Acute physiology and chronic health evaluation II (APACHE II) score and systemic inflammatory response syndrome (SIRS) were defined by the Atlanta classification. IAP was measured by bladder pressure measurement. IAP > 20 mmHg associated with new-onset organ failure or acute worsening of existing organ failure was defined as ACS. The major gastrointestinal events related to feeding were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS, version 16.0 for Windows (SPSS Inc., Chicago, IL). Data were expressed as means ±SD for normally distributed data. For normally distributed data, variables were compared using Student's t-test for 2 groups. For skewed data, the Mann-Whitney test was used. Qualitative or categorical variables were described as frequencies and proportions. Proportional variables were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. A two-tailed P<0.05 was considered to be statistically significant.

Results

From May 2014 to December 2015, a total of 312 patients were assessed for eligibility, and 108 of them were excluded based on the inclusion and exclusion criteria. Therefore, a total of 103 patients in the sham feeding group and 101 in the control group were included (Figure 1). The demographic data (age, sex, and etiology) from the 2 groups were comparable (Table 1). The etiology was mainly from hyperlipemia (39.8% in the sham feeding group and 36.6% in the control group) and gallstone (30.1% in the sham feeding group and 27.7% in the control group). In addition to the demographic data, the severity of AP in the sham feeding group was similar to that in the control group (P≥0.05). There was no difference between the 2 groups in the intervals from onset of symptoms to admission (P≥0.05). In addition, there was also no significant difference in the body-mass index (BMI) and serum albumin between the sham feeding group and the control group (P≥0.05).

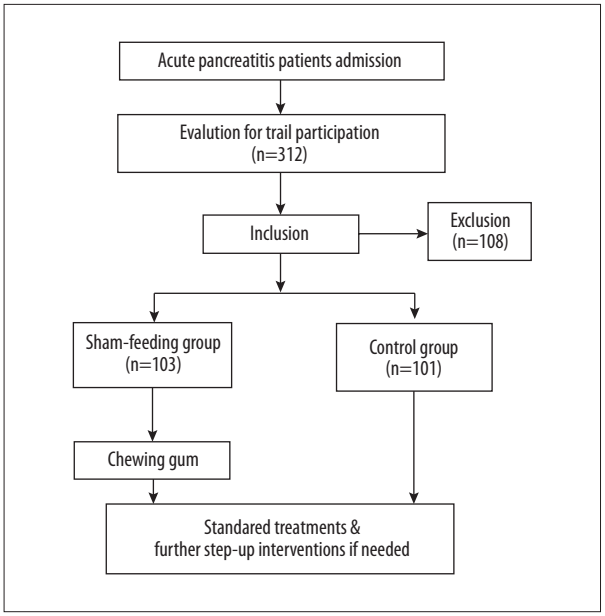

Figure 1. Flow diagram detailing development.

The clinical outcomes of both groups are detailed in Table 2. Although the mortality in the control group (5.9%) was slightly higher than that in the sham feeding group (4.9%), there was no significant difference between the 2 groups (P<0.05). There were also no differences between groups in the proportion of patients who developed infected necrosis and needed further interventions, which were 18.4% and 19.8%, respectively. The average LOS was 22.7 days for all patients. In the sham feeding group, the number of days in hospital were 21.9±15.9 and days in the ICU were 3.3±2.9. In the control group, the number of days in the ICU (3.6±3.1) was similar to the sham feeding group (P≥0.05), and the days spent in hospital (23.7±17.3) were more than that of the sham feeding group (P<0.05). The average total cost during hospitalization was significantly higher in the control group than in the sham feeding group (p<0.05). The results suggest that the patients instructed to chew gum recovered from pancreatitis more quickly but without better outcomes.

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Table 1. Demographics and characteristics of acute pancreatitis patients included in the analysis.

Characteristic	Sham feeding group (n=103)	Control group (n=101)	p Value
Age	49.8±13.9	50.1±13.1	0.73
Sex			0.46
Male (%)	62 (60.2)	64 (63.4)	
Female (%)	41 (39.8)	37 (36.6)	
Etiology			0.42
Gallstone (%)	31 (30.1)	28 (27.7)	
Alcohol abuse (%)	22 (31.3)	24 (23.8)	
Hyperlipemia (%)	41 (39.8)	37 (36.6)	
Other (%)	9 (8.7)	12 (11.9)	
Severity Scores			0.61
Mild pancreatitis	30 (29.1)	28 (27.7)	
Moderate severe pancreatitis	51 (49.5)	53 (52.5)	
Severe pancreatitis	22 (21.4)	20 (19.8)	
Days from onset of symptoms to admission, d	1.6±0.6	1.6±0.7	0.78
Body-Mass Index	25.2±4.1	25.3±3.9	0.62
Serum albumin, g/L	37.7±11.7	36.8±13.1	0.77

Table 2. Clinical outcomes in the 2 groups.

Characteristic	Sham feeding group (n=103)	Control group (n=101)	p Value
Mortality (%)	5 (4.9)	6 (5.9)	0.22
Developed Infected Necrosis and Needed Further Interventions	19 (18.4)	20 (19.8)	0.15
Length of stay			
Days in hospital, d	21.9±15.9	23.7±17.3	<0.01[a]
Days in ICU, d	3.3±2.9	3.6±3.1	0.77
Total cost during hospitalization, dollars	7746.3±1795.2	8224.7±2125.9	0.02[a]

[a] Significant difference.

The detailed gastroenteric functions and nutritional variables were also recorded (Table 3). The time to first flatus, time to passage of feces, and time to begin enteral feeding in the sham feeding group were all shorter than those in the control group (2.9±1.3 *vs.* 3.3±1.2, 4.1±2.1 *vs.* 4.8±1.9, 2.7±1.5 *vs.* 2.9±1.6, respectively). However, no differences were found between groups except in the time to passage of feces (P<0.05). The incidences of gastrointestinal adverse events after refeeding in the 2 groups were similar (P≥0.05), except for vomiting. The patients in the sham feeding group took less time to achieve their nutrition target (25 kcal/kg/d) and fully tolerated an oral diet (P<0.05). No differences were observed in the change of IAP and the incidence of ACS between both groups (P<0.05). Moreover, weight and serum albumin decreased more significantly 1 week after admission in the control group (P<0.05).

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Table 3. Gastroenteric functions and nutritional variables in the 2 groups.

Variable	Sham feeding group (n=103)	Control group (n=101)	p Value
Time to first flatus, d	2.9±1.3	3.3±1.2	0.09
Time to passage of feces, d	4.1±2.1	4.8±1.9	0.04[a]
Time to begin enteral feeding, d	2.7±1.5	2.9±1.6	0.87
Time to full tolerance of oral diet, d	4.3±1.8	4.7±2.3	0.03[a]
Time to achieve the energy target[b], d	7.3±1.9	8.5±2.3	<0.01[a]
Gastrointestinal events after refeeding			0.13
Nausea (%)	33 (32.0)	38 (37.6)	
Vomiting (%)	11 (10.7)	15 (14.9)	
Ileus (%)	14 (13.6)	16 (15.8)	
Diarrhea (%)	13 (12.6)	19 (18.8)	
Intra-Abdominal Pressure, mmHg			
Admission	10.3±4.3	10.7±4.8	0.28
1 week after admission	6.7±2.9	6.9±3.6	0.33
Abdominal compartment syndrome (%)	2 (1.9)	3 (2.9)	0.67
Weight loss (%)			0.03[a]
<5%	58 (56.3)	52 (51.5)	
≥5%	45 (43.7)	49 (48.5)	
Serum albumin after 1 week, g/L	29.3±10.3	27.8±11.1	0.04[a]

[a] Significant difference; [b] Energy target=25 kcal/kg/d.

Discussion

Decreased intestinal motility is commonly observed in clinical practice during the early stage of AP [3,24]. The etiology of this gastrointestinal disorder is believed to be multifactorial [4]. During this period, the fluid collections, which are rich in inflammatory factors, including TNF-α, IL-1, and IL-10, accumulate in the peritoneal cavity and around the retroperitoneal pancreatic space [25]. These fluid collections may stimulate retroperitoneal plexus and induce nerve reflex disorder [26]. Local tissue hypoxia prompted by blood flow redistribution induces gastrointestinal edema and weak smooth muscle motility [27,28]. In addition, inflammatory mediators such as vasoactive intestinal peptide, substance P, and nitric oxide are released in association with the stress response [29]. All of the above factors directly or indirectly contributed to the reduced bowel motility and ileus.

Decreased intestinal motility promotes the development of disease [5,30]. Once the intestinal motility decreases, digestive secretions and gases accumulate inside the bowel, leading to increased IAP [31]. An IAP higher than 20 mmHg may induce ACS and thus affect respiration and circulation functions [32]. In AP patients with accompanying ACS, the mortality rate drastically increases [6]. The decrease in intestinal motility can also result in delayed gastrointestinal emptying and subsequently induced nausea and vomiting, leading to electrolyte disturbance and acid-base imbalance [33]. In addition, research has confirmed that decreased intestinal motility is associated with an obvious imbalance of the intestinal flora [34,35]. The aerobic and anaerobic organisms become unbalanced and the normal bio-barrier is broken after intestinal motility decreases [36,37]. Decreased bowel movements and mucus flow are also more beneficial for the retention and reproduction of pathogenic bacteria [38]. Overgrown bacteria and endotoxin translocate intestinal mucosa and further induce the "second hit" [39]. Translocated bacteria and endotoxins activate monocytes and macrophages to release excessive cytokines and inflammatory mediators, possibly inducing SIRS [40]. In addition, early EN has been recognized as one of the most important treatments for AP, especially SAP [1]. Early EN has been proven to be related to suppression of negative nitrogen balance in the acute inflammation phase, the promoted restoration of the intestinal barrier function, and the decreased

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occurrence of enterogenous infection [41,42]. Furthermore, decreased gastric motility can also lead to the development of EN intolerance, causing delayed or failed EN [8]. However, EN has been reported to be associated with better clinical outcomes, and delayed or failed EN can result in a prolonged hospital stay and poor prognosis [43,44].

Therefore, reducing the incidence of intestinal motility disorders and promoting motility restoration has become a major research topic in the treatment of AP. Currently, there are several methods that have been described in the literature. For example, prokinetic agents (e.g., serotonin receptor agonists such as itopride) [45], traditional Chinese medicine (e.g., Da-Cheng-Qi decoction and Qing-Yi decoction) [46,47], and some mechanical stimulations (e.g., electrical stimulation) [48] have been proven to improve gastrointestinal motility in previous studies. However, the clinical safety, efficacy, and convenience of these strategies have not been well studied.

Sham feeding is a method used in ERAS for promoting the recovery of gastrointestinal motility [12,13]. Research has shown that sham feeding can activate the cephalic-vagal reflex and thus promote gastrointestinal motility by both humoral and nervous stimulation [14,15,49]. Gum chewing mimics food intake and is thought to be an inexpensive and convenient type of sham feeding [16]. It has also been suggested that the hexitols in sugar-free gum may play a role in resolving ileus through their osmotic effects [50]. At present, sham feeding via gum chewing has been utilized in postoperative management following multiple surgeries and has been proven to be safe and efficacious [13,16,51]. Therefore, we speculated that sham feeding might be safe and efficacious in the treatment of AP as well. We also considered that sham feeding had the potential to promote intestinal motility without significantly increasing the burden on the digestive tract, as well as preventing adverse gastrointestinal events.

According to our current study, the LOS and hospital costs for the sham feeding group were reduced, although there was no significant effect on mortality. Moreover, the incidence of gastrointestinal adverse events, including nausea, vomiting, abdominal pain, and diarrhea, significantly decreased in the sham feeding group. The implementation of EN also showed improvement in the sham feeding group. Compared with the control group, the sham feeding group was able to reach the nutritional targets (25 kcal/kg/d) earlier, with better nutritional indicators. Meanwhile, the proportion of patients who terminated or delayed EN because of EN intolerance was significantly lower in the sham feeding group. Thus, for the first time, we demonstrated the effectiveness and safety of sham feeding in patients with AP.

However, our study has some limitations. First, as a single-center study, the sample size was relatively small, which is a potential source of bias [52]. Second, the type of chewing gum was not uniformly required during the study design; as a result, the subjects chewed different types of gum, and the substances in the gum (e.g., with or without sugar) may have affected the results of the study [53]. Furthermore, the EN performed in our study was slightly different from that recommended in international guidelines [20,21]. Many current guidelines recommend that for patients with mild or moderate AP, no EN is needed, but for severe AP, EN should be started within the first 48 or 72 h after disease onset. In our clinical practice, however, intolerance to early EN (especially within 36 h after disease onset) is more common, which may be explained by differences in ethnicity or EN formula. Thus, in our current study, a relatively compromised EN formula was used. For patients with AP, clinicians with extensive clinical experience decided on the mode and starting time of EN based on disease conditions: oral feeding was applied for patients with mild AP, whereas tube feeding was applied for patients with more severe conditions. EN was typically started within 48–72 h after admission, which was slightly later than is recommended in the guidelines. Finally, the different EN strategies may also have interfered with the study results.

Conclusions

In summary, this prospective, randomized, controlled trial is the first to confirm that sham feeding is effective and safe for treating AP. In addition, other aspects (including pain management, minimally invasive surgery, early activities, and early EN) of ERAS may also be applicable in the clinical management of AP. With this in mind, in our future studies we will further investigate the application of ERAS in the management of AP.

Conflict of interest

The authors have no conflicts of interest to disclose.

Statement

None of sources of support were directly involved in the design of the study, or in the collection and analysis of the data in this report.

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