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Review Article

Comparison of nasogastric feeding versus nasojejunal feeding for severe acute pancreatitis: a systematic review and meta-analysis

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Abstract: Nasogastric (NG) and Nasojejunal (NJ) feeding are feasible ways in enteral nutrition (EN) of severe acute pancreatitis (SAP). However, which is the optimal approach has long been debated among experts. This meta-analysis was to examine the differences in efficacy and safety of the two routes for patients with SAP. We searched the Cochrane Library, PubMed, EM base Databases, Web of Science, Wanfang Data base, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM disc). Prospective clinical controlled trials comparing NG and NJ feeding in patients with SAP were eligible for inclusion. Total of 446 patients with SAP from nine clinical controlled trials were identified and included in our study, involving 229 patients in NGEN group and 217 in NJEN group. There were no significant differences between the two groups in the risk of mortality, infectious complications, exacerbation of pain, diarrhoea, tube displacement, conversion to surgery, intolerance of feeding, achievement of energy balance. Nasogastric feeding was considered effective and well tolerated when compared with nasojejunal feeding through this meta, and the former is more economical and convenient. NG feeding, which eases the administration of enteral nutrients in the clinical setting, may be the preferred way in patients with SAP.

Keywords: Severe acute pancreatitis, nasogastric, nasojejunal, enteral nutrition, meta-analysis

Introduction

Severe acute pancreatitis (SAP) [1, 2] is a common emergency and critical disease, characterized by high mortality rates and increasing incidence worldwide. The patients in SAP are in a hypermetabolic status, leading to critically malnutrition, impaired immune function and increasing risk of bacteria translocation [3]. Nutritional support [4] plays an important role in the management of SAP. Enteral nutrition (EN) [5, 6] was comprehensively recommended in the treatment of SAP, which can restore intestinal permeability, enhance immunity and decrease infectious complications.

The benefits of enteral nutrition in patients with SAP are well advocated and accepted, but the method of providing nutrition for patients with SAP remains controversial [7]. EN can be given either through the nasogastric (NG) or the nasojejunal (NJ) routes. Conventionally, NJ feeding is much more commonly employed in clinical practice. The placement of NJ tube is a cumbersome routine procedure requiring the assistance of endoscope or fluoroscope, but only a few hospital centers can provide the medical equipment at the bedside. What is worse, it may cause a delay in the commencement of early enteral feeding and affect the clinical outcomes. In contrast, NG feeding can be advantageous as the tube placement is convenient and simple [8].

At the beginning of the 21st century, Eatock *et al* [9] carried out one of the earliest prospective studies, demonstrated that NG feeding was feasible, which prompted more clinical controlled trials to assess the application of NG tube. In recent years, some new well-designed and sufficiently powered RCTs on NG versus NJ feeding were launched. The quality of meta-analysis depends on the quality of included studies. Given that this review incorporated the

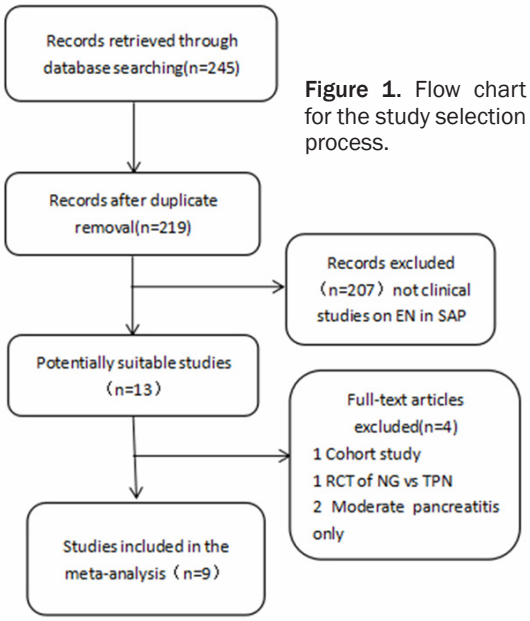

Figure 1. Flow chart for the study selection process.

latest and more trials than previous papers in this area and it provided a more well-rounded global perspective without the limitation of age, race, and sex. Therefore, our meta-analysis was to perform a more valuable evaluation for NG nutrition and NJ nutrition with respect to mortality, adverse events associated with nutrition, infectious complication and the delivery of nutrition by aggregating the reported data across the multivariate studies.

Material and methods

Search strategy

We searched the Cochrane Library, PubMed, EM base Databases, Web of Science, Wanfang Database, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM disc) for all the relevant articles about NG feeding from Dec. 2000 to Dec. 2015, using the terms "nasogastric", "nasojejunal", "tube feeding", "enteral nutrition", "pancreatitis" and their analogues. Reference lists of all included articles were scrutinized to disclose additional literature on this topic. There were no restrictions on publication language.

Inclusion and exclusion criteria

This meta-analysis only included studies meeting the following criteria: (1) clinical controlled trials fully reported with detailed information available; (2) population: patients eligible for inclusion were adults (aged 18 years) with predicted SAP according to the newest criteria of the Atlanta 2012 classification [10] or guidelines of the Chinese medical association of acute pancreatitis clinical diagnosis and classification standard of 2013 [11]; (3) intervention: NG feeding versus NJ feeding; (4) outcome measures: the primary outcome is mortality, and at least one of the following variables: infectious complications, diarrhoea, exacerbation of pain and need for surgical intervention, tube displacement, intolerance of feeding, achievement of energy balance. Exclusion criteria included: (1) case report, review, meta-analysis, guideline or experiments on animals; (2) duplicate publications; (3) not reporting clinical relevant outcomes or not providing enough details; (4) lack of control group.

Quality assessment

The quality of the included studies was assessed using the Cochrance handbook 5.0 [12]. The following information was evaluated: (1) random sequence generation; (2) allocation concealment; (3) double blinding process; (4) the description of withdrawals or dropouts and intentional analysis, incomplete outcome data, selective reporting and other bias.

Data extraction

Two investigators independently (Ying-Jie Guo, Xue Jing) screened titles and abstracts of all relevant articles according to predetermined inclusion criteria and extracted the data from each included study and disagreements were settled by discussion among all investigators. The main outcomes of interest were mortality, adverse events associated with nutrition, infectious complication and the delivery of nutritional. For each study, the following data were extracted: first author's name, publication year, study design, sample size, country and baseline characteristics in the multivariate statistical analysis.

Statistical analysis

The Cochrane Collaboration's Review Manager Software 5.3 (RevMan 5.3) was used for the meta-analysis. The differences between the NG and NJ groups were expressed as the risk ratio (RR) or mean difference with its 95% confidence interval (CI). Heterogeneity was mea-

Table 1. Characteristics of the studies included

Reference	Year	Region	Design	Sample size	Feeding start	Final analysis indicators
Eatock [14]	2005	Scotland	RCT	49	<72 hours after onset	①③④⑤⑦⑧
Kumar [15]	2006	India	RCT	30	48-72 hoursof admission	①②③④⑤⑥⑦⑧⑨
Singh [16]	2012	India	RCT	78	48 hours of admission	①②③④⑥⑧⑨
Piciucchi [17]	2010	Italy	Pragmatic	25	4 days of admission	②③④⑤⑧
Jiang RL [18]	2011	China	RCT	27	7-11 days after onset	①③⑦
Xiaoli LY [19]	2011	China	RCT	43	<24 hours after onset	②
Ouyang YX [20]	2011	China	RCT	54	4±2 days of admission	②④⑥⑨
Du ZH [21]	2015	China	RCT	80	18-19 hours after onset	②③④⑧⑨
Luo XJ [22]	2015	China	RCT	60	48-72 hours of admission	①②③④⑨

① mortality; ② infectious complications; ③ exacerbation of pain; ④ diarrhoea; ⑤ tube displacemen; ⑥ conversion to surgery; ⑦ intolerance of feeding; ⑧ achievement of energy balance; ⑨ aspiration pneumonia.

Table 2. Patient characteristics of participants in studies included in the meta-analysis

Reference	Group	No. of patients	Age (year)	Male (case)	Etiology			APACHE II score	Total hospital stay (days)
					Biliary	Alcohol	Idiopathic or other		
Eatock [14]	NG	27	63 (24_74)*	14	16	6	3	10 (7-18)*	16 (10-22)*
	NJ	22	58 (48_64)*	12	16	6	0	12 (8-14)*	15 (10-24)*
Kumar [15]	NG	16	43.25±12.76†	11	7	4	5	10.5±3.8†	24.06±14.35†
	NJ	14	35.57±12.5†	14	4	4	5	9.6±5.0†	29.93±25.54†
Singh [16]	NG	39	39	28	12	12	15	8.5 (2-19)*	17 (1-73)*
	NJ	39	40	25	21	10	9	8 (2-24)*	18 (4-54)*
Piciucchi [17]	NG	15	56 (31-83)*	9	6	9	-	-	30.6 (18.1-43)*
	NJ	10	63 (36-89)*	6	5	5	-	-	21.2 (17.7-24.6)*
Jiang RL [18]	NG	14	53.7±13.2†	11	8	1	5	12.3±8.5†	59.8±15.6†
	NJ	13	53.7±15.4†	9	8	1	4	11.8±7.6†	46.0±11.8†
Xiaoli LY [19]	NG	22	42 (34-58)*	12	18	0	4	18 (13-28)*	-
	NJ	21	44 (36-62)*	11	18	0	3	17 (14-26)*	-
Ouyang YX [20]	NG	27	31.5±10.6†	12	-	-	-	-	19.4±1.6†
	NJ	27	31.5±10.6†	10	-	-	-	-	20.5±1.2†
Du ZH [21]	NG	40	41 (25-60)*	23	13	20	7	17 (13-27)*	28±5†
	NJ	40	43 (23-65)*	22	12	20	8	16 (12-28)*	27±4†
Luo XJ [22]	NG	30	53.7±13.7†	10	14	6	10	5.1±2.1†	20.8±8.2†
	NJ	30	50.2±13.5†	8	17	4	11	4.5±2.6†	21.5±9.3†

*Values are median (range); †Values are mean ± standard deviation.

sured using the I^2 test and was considered significant when the I^2 value was above 50% and $P<0.05$. I^2 is the proportion of total variation contributed by between-study variability. In the presence of statistical heterogeneity, a random-effect model was used. In the absence of statistical heterogeneity, the fixed-effect model was used [13].

Results

Search results and study characteristics

The database search yielded 245 articles, after exclusion of duplicates, 219 records were screened. Full-text articles were retrieved for 13 potentially suitable studies, of which 4 were excluded. **Figure 1** detailed the selection process and the reasons for study exclusion. Ultimately, 9 clinical studies [14-22] fulfilled the inclusion criteria for consideration in our meta-analysis. Eight were RCTs and one was a non-randomised pragmatic study [17]. The included studies spanned the period from December 2000 to December 2015, two studies were from India [15, 16], one was from Scotland [14], and one was from Italy [17], the other five were from China [18-22]. Of our studies, 446 participants were included, 229 were assigned to NG

Table 3. Quality of included studies

Reference	Randomization method	Double blind	Withdrawals and dropouts	ITT method	Baseline	Quality grade
Eatock [14]	Computer generated random numbers	No	2	Yes	Similar	A
Kumar [15]	Computer generated random numbers	No	1	Unclear	Similar	B
Singh [16]	Random number table	No	2	Yes	Similar	A
Piciucchi [17]	None	No	3	Unclear	Similar	C
Jiang RL [18]	Not specified	No	4	Yes	Similar	B
Xiaoli LY [19]	Not specified	No	0	Yes	Similar	B
Ouyang YX [20]	Not specified	No	0	Unclear	Similar	C
Du ZH [21]	Not specified	No	0	Yes	Similar	A
Luo XJ [22]	Random number table	No	0	Yes	Similar	B

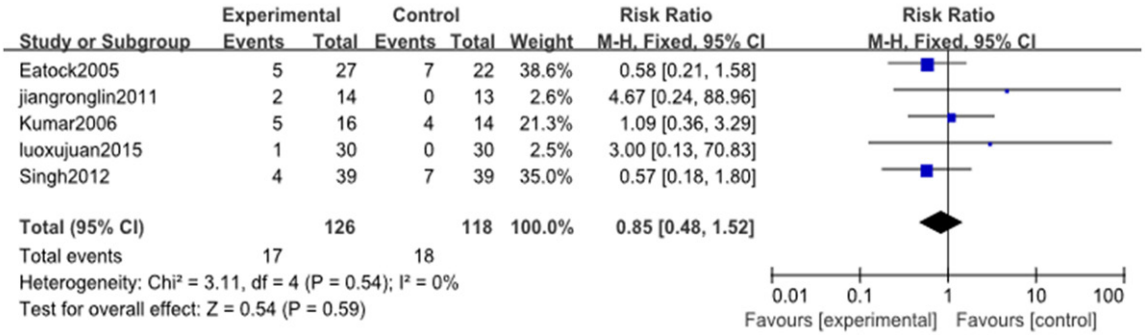

Figure 2. Comparison of mortality between NG feeding and NJ feeding groups.

group and 217 to NJ group. A summary of study characteristics is presented in **Table 1**. The baseline demographic data of the patients receiving the NG and NJ approaches were comparable (**Table 2**). The risk of bias assessments showed that most of these studies were of moderate quality (**Table 3**).

Meta-analysis of NG vs. NJ

Mortality: Four included trials (244 cases) reported the mortality. The overall mortality rate of NG route group and NJ route group was 12.5% (17/136) and 15.2% (18/118) respectively, which is consistent with the previous reported rate [23]. There was no significant heterogeneity among these studies (P=0.54, I^2= 0%), the fixed effect model was used for data analysis. Meta-analysis showed no significant difference in mortality between NGEN and NJEN groups [RR=0.85, 95% CI (0.48, 1.52), P=0.59] (**Figure 2**).

Infectious complications: With respect to the infectious complication, seven included trials (350 cases) reported the occurrence of any infectious complication in blood, pancreatic tissue, bile and tracheal aspirate during hospital stay. Sepsis, aspiration pneumonia, pancreatic necrosis and organ failure have been reported by Singh, Kumar [15, 16]. Jiang RL [18] reported one case with pancreatic pseudocyst observed in the NG nutrition group, one case with pulmonary infection in NJ group. The number of infectious events was similar between the two groups in the included studies. No heterogeneity (P=0.17, I^2=34%) was observed between the research results for all comparisons, therefore, a fixed effect model was used. There were no significant differences in infectious complications between NGEN and NJEN groups [RR=0.84, 95% CI (0.61, 1.16), P=0.28] (**Figure 3**). Five trials provided information regarding aspiration pneumonia, a subgroup analysis is available. NG feeding has been believed to increases the chances of aspiration pneumonia [24]. However, this was not observed in our study [RR=1.23, 95% CI (0.60, 2.50), P=0.57] (**Figure 4**).

Recurrence or exacerbation of pain: Seven included trials (349 cases) reported detailed

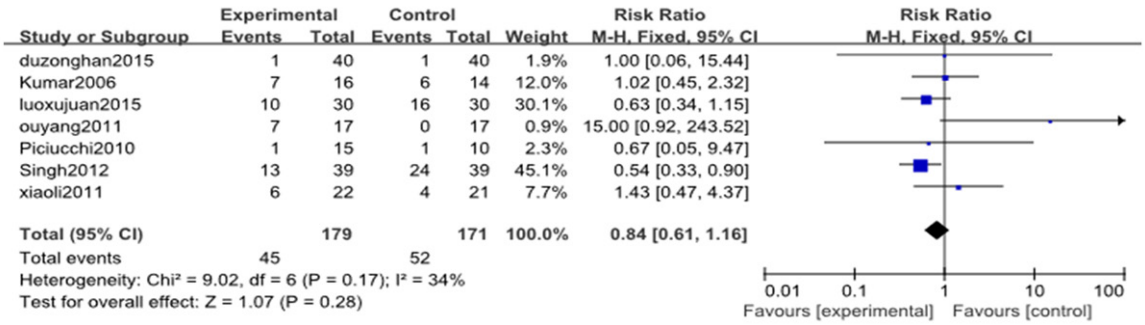

Figure 3. Comparison of infectious complications between NG feeding and NJ feeding groups.

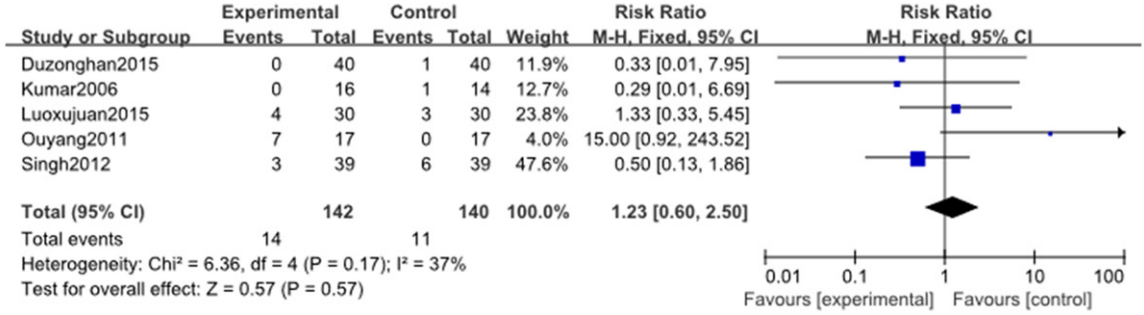

Figure 4. Comparison of aspiration pneumonia between NG feeding and NJ feeding groups.

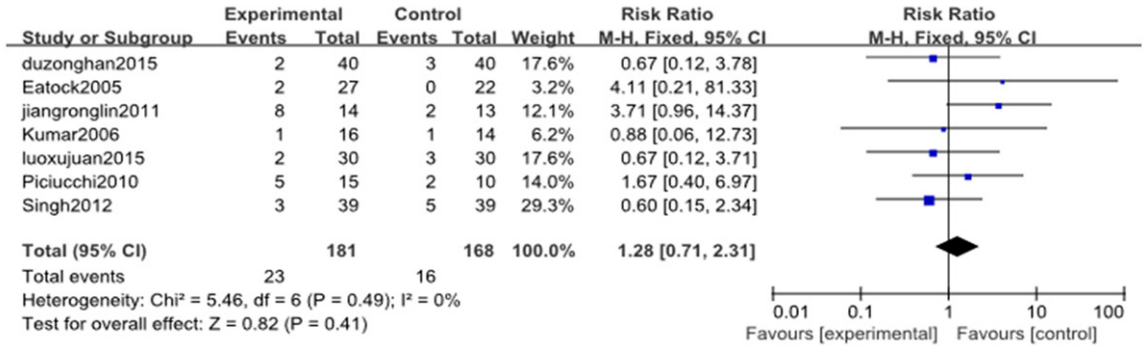

Figure 5. Comparison of exacerbation of pain between NG feeding and NJ feeding groups.

data on the circumstance of pain, 23 patients out of 181 (12.7%) experienced an recurrence or exacerbation of pain after commencement of nutrition, but few cases withdrawal of the enteral feeding just due to an aggravate pain. Pain can be relieved effectively by adjusting speed and quantity of nutrition solution, such as tube feeding can be given as a slower infusion at a rate of 1 to 1.5 mL/min. In the study by Singh *et al* [16], only 3 patients in the NG group, and 5 patients in the NJ group had recurrence of pain which was not associated with any significant rise in serum amylase or worsening of pancreatitis. Similarly, Petrov MS [23] reported only 4.3% patients experienced an exacerbation of pain after route feeding. No heterogeneity was detected (P=0.49, I^2=0%), the fixed effect model was used. The results of meta-analysis showed no significant difference in this part between NGEN and NJEN groups [RR=1.28, 95% CI (0.71, 2.31), P=0.41] (**Figure 5**).

The risk ratio of diarrhea: Diarrhoea was one of the most common nutrition associated adverse events. A pooled analysis of seven stud-

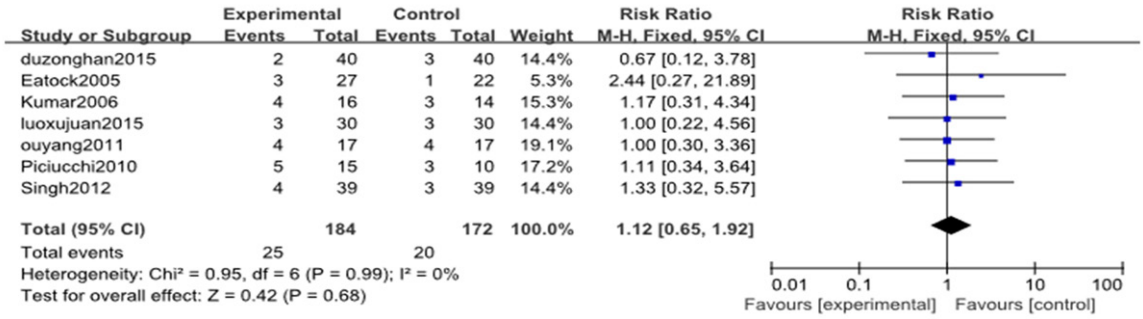

Figure 6. Comparison of diarrhoea between NG feeding and NJ feeding groups.

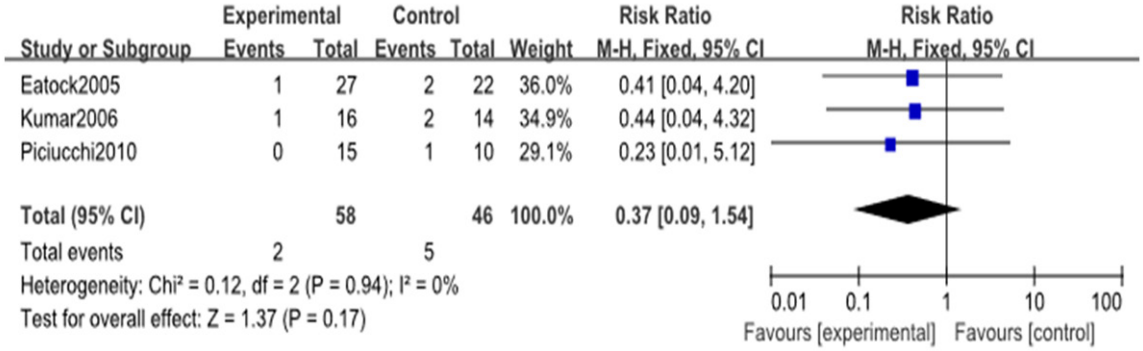

Figure 7. Comparison of tube displacemen between NG feeding and NJ feeding groups.

ies enrolling 356 patients revealed the occurrence of diarrhea. Signs of heterogeneity was not found across trials (P=0.99, I^2=0%), and a fixed effect model was used. The results of meta-analysis showed no significant difference in this part between the two groups [RR=1.12, 95% CI (0.65, 1.92), P=0.68] (**Figure 6**).

Tube displacement: Only three included studies enrolling 104 patients included reported the occurrence of tube displacement. No heterogeneity was detected (P=0.94, I^2=0%), fixed effect model was applied to process data. The pooled risk ratios for the outcome suggest that there was no significant difference between the NG and NJ group [RR=0.37, 95% CI (0.09, 1.54), P=0.17] (**Figure 7**). A study by Piciucchi *et al* [17] showed that 40% (which occurred in 15 of the 25 patients) of the NG tubes spontaneously migrated to the jejunum (beyond Treitz' ligament). In our included studies, position of the tube was not constantly monitored. Considering these restrictions, accidental tube removal such as the circumstance of nutrient canal falling off was mainly involved in our study. Further studies are expected.

Surgical intervention: Three included trials (162 cases) reported the rate of surgery, seven patients underwent surgery in the NG group, four in the NJ group. For example, in the study by Kumar [15], only two patients with NJ and one patient with NG feeding had surgery for infected necrosis. No heterogeneity was detected (P=0.89, I^2=0%) and meta-analysis showed no significant difference in this part [RR=1.81, 95% CI (0.56, 5.92), P=0.32] (**Figure 8**).

Intolerance of feeding: Three included trials (106 cases) reported the risk of switch to TPN as failed to tolerate EN feeding treatment. Jiang RL *et al* [18] reported four cases required withdraw feeding due to blood amylase up to 2 times higher than before in NG route group. The possibility of upper gastrointestinal tract obstructions or gastric dysmotility could not be ruled out. It may need a process of adaptation to NG nutrition. No heterogeneity was detected (P=0.40, I^2=0%), the fixed effects model was used. A pooled data of indicated that NG feeding was more likely to lead to intolerance of feeding, but this difference was not statistica-

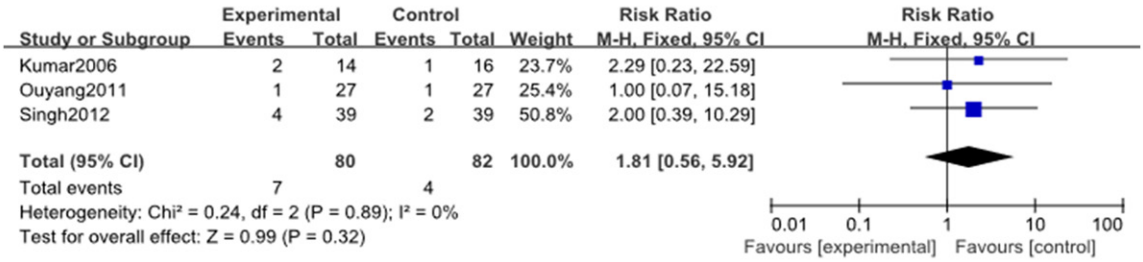

Figure 8. Comparison of tube conversion to surgery between NG feeding and NJ feeding groups.

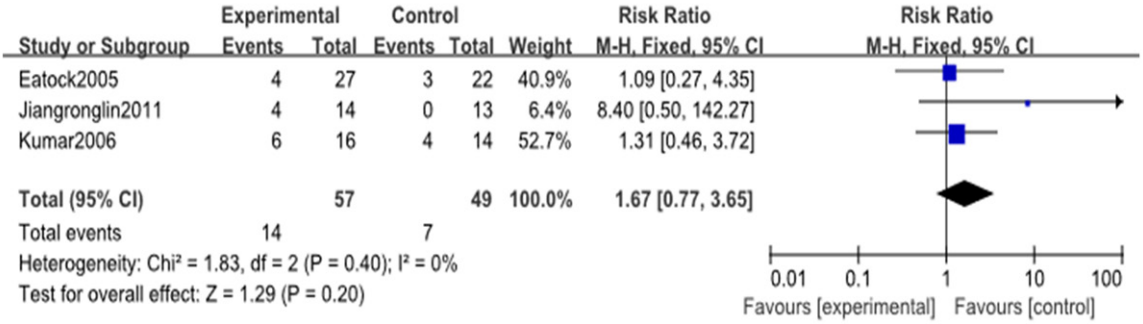

Figure 9. Comparison of intolerance of feeding between NG feeding and NJ feeding groups.

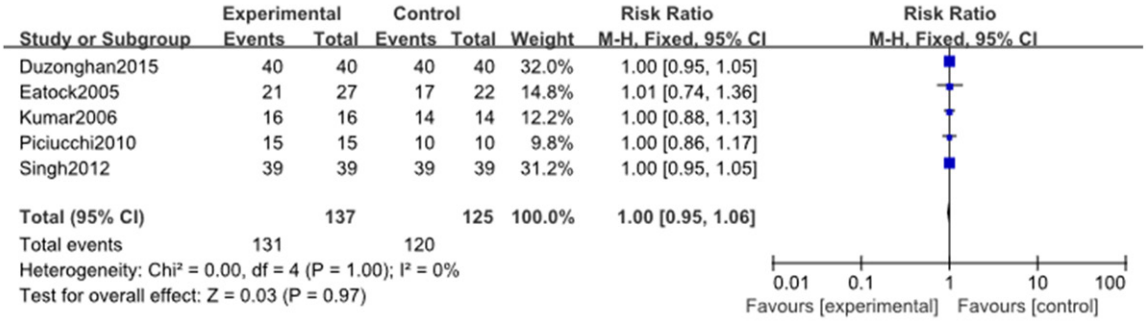

Figure 10. Comparison of achievement of energy balance between NG feeding.

lly significant [RR=1.67, 95% CI (0.77, 3.65), P=0.20] (**Figure 9**).

Achievement of energy balance: In the eligible trials, five included trials (262 cases) reported the index, of the 137 patients assigned to the NG group, 131 (95.6%) achieved the nutritional targets, in contrast, 120 (96.0%) in the NJ group (125 cases). The nutritional targets set by the investigators were not complete coincident, for example, in the study by Kumar *et al* [15], the achievement of energy balance was defined by patients reaching a goal of 1800 kcal within seven days after the start of feeding, while in the study by Singh *et al* [16] and Du ZH *et al* [21], the energetic target was 25-30 kcal/(kg·d). No heterogeneity was detected (P=1, I^2=0%), in the fixed effects model, the meta-analysis showed that there was no significant difference between the two routes in the delivery of nutrition. NG delivery of enteral nutrition to patients with severe AP was efficacious [RR=1.00, 95% CI (0.95, 1.06), P=0.97] (**Figure 10**).

Discussion

Enteral nutritional management for SAP has been regarded as a crucial issue. Our meta-analysis did not find any significant difference

in NG feeding and NJ feeding for SAP. In fact, arguments against NG route are based on the effect of stimulating pancreatic secretion. However, some studies [25, 26] suggested that pancreatic exocrine function diminish significantly in AP patients compared with healthy subjects and the secretion function is negatively correlation with the severity of AP. These studies may provide some theoretical support for the clinical application of NG approach.

The severity of pancreatitis is an important indicator for nutrition management decision-making. For example, oral feeding can be recommenced in mild pancreatitis once pain and nausea have resolved by the new guidelines [27, 28]. Previously, severity had been classified into mild and severe forms according to the 1992 Atlanta classification. However, in the newly revision (Atlanta 2012 classification), moderately severe acute pancreatitis is distinct from severe pancreatitis. The inclusion criteria of SAP are not completely consistent among the included studies, and old criteria for diagnosing SAP, which may include some patients with moderate SAP. As a result, patient characteristics may differ between these trials and it may result in some bias.

Until now, some meta-analyses [23, 29, 30] of trials of NG feeding in SAP patients are acquired. In the latest systematic meta-analysis published by Youfeng Zhu *et al* [30], four randomized controlled trials involving 237 patients were pooled for the analysis, did not demonstrate a statistically significant difference between the NG and NJ routes in regard to mortality, infectious complications, digestive complications, achievement of energy balance, or length of hospital stay. With a total of 446 patients and nine clinical controlled trials being eligible for meta-analysis, our study incorporates the most current research and analyzed more variables, increasing the confidence with which conclusions can be drawn. This review had shown similar results, but we analyzed more variables such as the circumstances of tube displacement, surgical intervention, intolerance of feeding, exacerbation of pain and the risk ratio of diarrhea. No significant differences were observed in these additional indexes between the two groups. Besides, in the study of Zhu YF *et al* [30], no heterogeneity was observed between the research results for all comparisons, a fixed effect model should be used, but they used the random effects model. Although it does not make the decisive influence on the conclusion, some bias on the confidence interval may be caused.

Though most of the studies indicate the equivalence between the NG and NJ groups, some conflicting outcomes have been reported. A recent randomised controlled trial by Jiang RL [18] suggest NJ feeding is superior to NG feeding by comparing the disease progresses, relevant inspection index and main symptoms. In his study, a total of 27 patients with SAP were randomized to receive feeding by either NG routes (14 patients) or NJ routes (13 patients). Baseline demographic parameters of all subjects in the RCTs were similar, but patients recover slowly in the index such as amylase, lipase and CRP and the symptom of bellyache in NG groups. Four cases dropped out of the trial as failed to tolerate NG feeding treatment. Highly individual and specialized management may be required in the nutrition support considering the potential of gastric dysmotility. Besides, it should not be ignored that the sample number is small in this clinical test.

American college of gastroenterology [31] has recommend NG feeding in patients with SAP. Some researchers even investigate the impact of NG feeding on the quality of life and suggest NG route is a well tolerated approach [32]. Nevertheless, the application of NG feeding in SAP has not been widely adopted worldwide. Our study was carried out to analyze the most current research from a global perspective and the results was encouraging by showing no significant differences between NG and NJ feeding in patients with SAP. Being the case, NG feeding route is comparable to NJ route in safety and efficacy, and has the prospect of taking the place of NJ feeding.

Our meta-analysis had several limitations. Firstly, the sample size in our meta-analysis was small. Secondly, not all the articles included were RCTs. Piciucchi *et al* [17] carried a non-randomised pragmatic study, continuous monitoring by serial X-rays for three days after feeding tube was placed, the patient was allocated lies on the final location of tube. Thirdly, because of the different feeding routes, it was hard to conduct double-blinded RCTs. But the clinical indexes we chose, such as the incidence of infection complications, were seldom affected by subjective feelings.

In summary, results from this meta-analysis suggested that NG feeding, which eases the administration of enteral nutrients in the clinical setting, would be as effective and safe as NJ in patients with SAP.

Disclosure of conflict of interest

None.

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