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Review

Braun enteroenterostomy reduces delayed gastric emptying: A systematic review and meta-analysis

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HIGHLIGHTS

- Braun enteroenterostomy reduces delayed gastric emptying following PD.
- Braun enteroenterostomy also reduces overall morbidity and length of hospital stay.
- No difference in other complications between BEE and traditional gastrojejunostomy.

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ABSTRACT

Background: It remains controversial whether the additional Braun enteroenterostomy (BEE) is necessary in decreasing delayed gastric emptying (DGE) following pancreaticoduodenectomy (PD). This meta-analysis aims to assess the efficacy of the additional BEE in reducing DGE after PD.

Methods: PubMed, EMBASE, Science Citation Index and The Cochrane Library were searched to identify relevant studies. Articles published before May 15, 2015 comparing BEE with traditional gastrojejunostomy during PD were selected. The evaluated end points consist of intro-operative outcomes as well as postoperative complications.

Results: Seven observational clinical studies that recruited 1401 patients were included. This meta-analysis indicated that the occurrence of DGE was lower in Braun group (odds ratio [OR], 0.30; 95% confidence interval [CI], 0.15 to 0.60; P = 0.0007). Overall morbidity (OR, 0.61; 95%CI, 0.47 to 0.80; P = 0.0003) and the length of hospital stay (LOS) (weighted mean difference [WMD], −1.80; 95%CI, −3.4 to −0.18; p = 0.03) were also in favor of the Braun group. However, Braun group had no advantage over Non-Braun group in terms of intra-operative blood loss, mortality, pancreatic fistula, bile Leakage and intra-abdominal abscess.

Conclusion: The additional of BEE plays an important role in reducing DGE, overall morbidity and LOS.

1. Introduction

Since its first performance by Codivilla [1] in 1898 and its later development by Whipple [2] in 1935, pancreaticoduodenectomy (PD) has served as the standard treatment for both malignant and benign diseases of pancreatic head and periampullary region for many years. With the advancement of surgical technology, the perioperative mortality of PD has significantly declined to below 5% [3]. However, the postoperative morbidity rate remains high (30%–50%) [4,5]. More recently, surgeons have placed much focus on the life-threatening complications such as pancreatic fistula, but yet, there seems to be scarce emphasis on the nonfatal complications. Apart from pancreatic fistula and postoperative hemorrhage, delayed gastric emptying (DGE) is one of the major troublesome complications after PD, the incidence of which ranges from 19% to 57% [6]. DGE is not fatal, but it can prolong the length of hospital stay (LOS), increase costs, and affect quality of life as well as nutritional status of patients [7]. Thus, it is of great importance to search for some more feasible and effective methods to reduce the incidence of DGE following PD.

Until now, surgeons have paid more attention to the post-operative morbidity associated with gastrojejunostomy (GJ). Several previous studies [8,9] indicated that the surgical technique factors of GJ were related to the incidence of DGE. Over one

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hundred years ago, Braun [10] introduced a modified technique of GJ, in which an anastomosis between the afferent and efferent limbs of jejunum distal to the gastroenterostomy was performed. Owing to an extra stoma, bile and food are more easily move down to the jejunum. As a result, this kind of modified GJ can decrease bile vomiting and bile reflux gastritis [11]. More recently, few articles [12,13] have focused on the influence of Braun enteroenterostomy (BEE) on the occurrence of DGE. However, no general agreement exists as to whether the additional BEE during PD is necessary in reducing DGE following PD. Therefore, it is needed to conduct a systematic and comprehensive analysis of those previous studies, and to evaluate the utility of performing BEE during this surgical procedure.

2. Methods

2.1. Inclusion and exclusion criteria

Studies met the following inclusion criteria were included: (1) clinical study and published in English, (2) the research object was the patients who underwent PD, (3) compare an additional BEE with traditional reconstruction of gastrojejunostomy, (4) provide the original data, including the incidence of DGE and other perioperative outcomes. Studies were excluded as follows: (1) abstracts, reviews, case reports and comments, (2) no control group, (3) lack appropriate data for extraction, (4) sample size was less than 20 patients.

2.2. Search strategies and study selection

PubMed, EMBASE, Science Citation Index and The Cochrane Library were searched to identify relevant studies. The search terms included “Braun enteroenterostomy”, “Braun”, “enteroenterostomy”, “delayed gastric emptying”, “pancreaticoduodenectomy”, and “gastrojejunostomy”. The references lists of selected studies were also searched to ensure that no potential studies were neglected. Two investigators (M.-Q.H. and M.L.) independently read the title and abstract of potentially eligible studies. The full texts of all eligible articles were then screened for detailed evaluation. Differences of opinion in the selection process were resolved by consensus. If failed to reach an agreement, the final decision would be made by a third investigator (B.-L.T.).

2.3. Outcome measures

The primary outcome was the occurrence of DGE, which was graded as grade A, grade B and grade C [6]. The secondary outcomes were overall morbidity, intra-operative blood loss, mortality, pancreatic fistula, bile leak, intra-abdominal abscess and the LOS.

2.4. Data extraction and quality assessment

Two researchers (M.-Q.H. and J.-Y.M.) independently extracted following data from all selected articles: first author, country, study period, study design, characteristics of enrolled patients, Definition of DGE, details of surgical procedure, intro-operative outcomes and postoperative complications. The quality of the extracted data was then adjudicated by a third researcher (B.-L.T.). The Newcastle-Ottawa scale (NOS) was conducted to evaluate the quality of the included studies [14]. The maximum “stars” obtained for “Selection”, “Comparability” and “Outcome” categories were 4, 2 and 3, respectively. A study which got at least 6 “stars” was considered high in quality [15].

2.5. Statistical analysis

Meta-analysis was carried out using Review Manager Version 5.3 software (The Cochrane Collaboration). Odds ratio (OR) and weighted mean difference (WMD) were chosen as summary statistic to dichotomous variables and continuous variables respectively. Both OR and WMD reported along with 95% confidence intervals (CI), with statistically significance set at $P < 0.05$. Heterogeneity was measured with χ^2 test and I^2 values. Low heterogeneity was defined as an $I^2 < 33\%$ [16]. Either random-effects model or fixed-effects model was used to calculate the combined outcomes according to heterogeneity. Furthermore, Sensitivity analysis and subgroup analysis were performed to explore the reasons for statistical heterogeneity, and to evaluate the impact of various types of design in the included trails. Publication bias was identified using funnel plot analyses [17].

3. Results

3.1. Literature search and study selection

Initially, a total of 791 articles were identified through literature search in PubMed, EMBASE, Science Citation Index and The Cochrane Library. We excluded 771 articles after screening titles and abstracts, in which 369 were duplicated and 402 were irrelevant. The remaining 20 articles were retrieved for more detailed evaluation. Among these 20 articles, 13 were excluded for various reasons as shown in the flow diagram (Fig. 1). Finally, seven appropriate studies were included for further analysis: three prospective observational clinical studies (OCS) [12,13,18] and four retrospective OCS [10,19–21].

3.2. Description of studies

The general characteristics were summarized in Table 1. A total of 1401 patients were enrolled: 875 in the Braun group and 526 in the Non-Braun group. The sample size of included studies ranged from 44 to 395 patients. No statistical difference was seen between Braun group and Non-Braun group in terms of age, sex and diabetes. The results of quality assessment were displayed in Table 2. All included references were high-quality studies, which got more than or equal to 6 “stars” based on the NOS criteria.

3.3. Definition of the complications

DGE was defined and graded by International Study Group of Pancreatic Surgery (ISGPS) criteria [6] as follows: grade A, unable to tolerate solid oral intake by the end of the postoperative day (POD) 7 and requiring nasogastric tube (NGT) between day 4 and 7 postoperatively; Grade B and Grade C were defined as inability to tolerate solid oral intake by the end of the POD 14 and POD 21, respectively. Overall morbidity was defined as total of perioperative complications. Mortality was defined as death within 30 days after surgery. Pancreatic fistula was defined according to International Study Group on Pancreatic Fistula (ISGPF) [5]. Other complications were defined based on Dind's report [22].

3.4. Meta-analysis of the perioperative outcomes

The results of meta-analysis of the operative outcomes and postoperative complications in all included studies were summarized in Table 3.

3.4.1. Delayed gastric emptying

All of the included studies reported DGE. The incidence of DGE

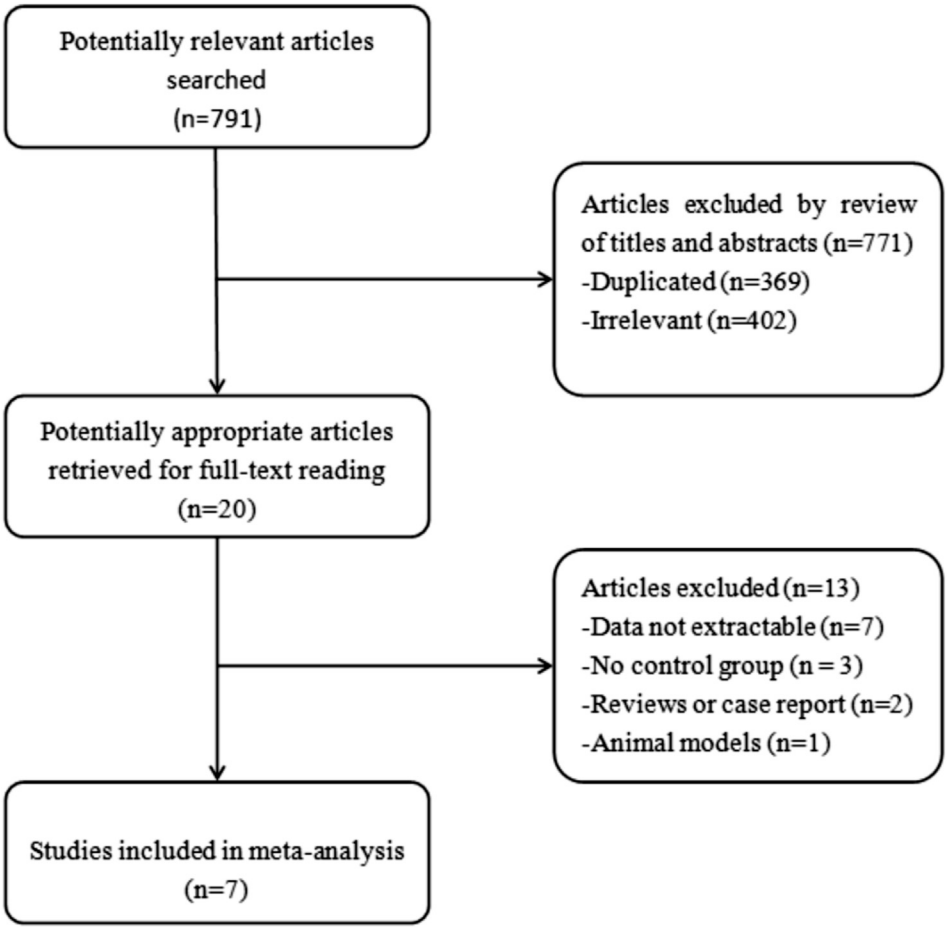

Fig. 1. Flow diagram of the studies identified in this meta-analysis.

Table 1
General characteristics of included studies.

Author	Country	Study period	Design	Group	Patients	M/F	Age (year)	Diabetes	Definition of DGE
Hochwald et al. [12]	USA	2001–2006	PNR	Braun	70	NM	65	NM	ISGPS
				Non-Braun	35		64		
Nikfarjam et al. [13]	Australia	2009–2011	PNR	Braun	24	15/9	67 (45–81)	7	ISGPS
				Non-Braun	20	14/6	70 (50–84)	7	
Wang et al. [19]	China	2008–2012	Retro	Braun	32	17/15	58.3 ± 5.7	5	ISGPS
				Non-Braun	30	19/11	56.6 ± 7.1	3	
Xu et al. [20]	China	2000–2013	Retro	Braun	206	124/82	57.88 ± 10.61	NM	ISGPS
				Non-Braun	201	128/73	58.13 ± 11.26		
Watanabe et al. [21]	Japan	2008–2013	Retro	Braun	98	57/41	67 (22–85)	21	ISGPS
				Non-Braun	87	47/40	70 (27–91)	19	
Zhang et al. [10]	China	2009–2013	Retro	Braun	347	271/73	57 ± 0.6	32	ISGPS
				Non-Braun	48	22/26	58 ± 2.8	8	
Meng et al. [18]	China	2009–2014	PNR	Braun	98	57/41	61.95	10	ISGPS
				Non-Braun	105	68/37	60.3	9	

PNR = prospective nonrandomized; Retro = retrospective; NM = not mentioned; M/F = male/female; ISGPS = International Study Group of Pancreatic Surgery criteria.

Table 2
Newcastle-Ottawa scoring system for non-randomized controlled trials.

Author	Selection (star)	Comparability (star)	Outcome (star)	Total (star)
Hochwald et al. [12]	4	1	2	7
Nikfarjam et al. [13]	4	2	2	8
Wang et al. [19]	3	2	3	8
Xu et al. [20]	3	1	2	6
Watanabe et al. [21]	3	2	2	7
Zhang et al. [10]	3	1	2	6
Meng et al. [18]	4	1	3	8

Table 3
Summary results of Braun vs Non-Braun during pancreaticoduodenectomy.

Outcomes	Studies (n)	Patients (n)		OR or WMD	95%CI	*P* value	Heterogeneity (I^2)
		Braun	Non-Braun				
DGE	7 [10,12,13,18–21]	73/875	116/526	0.30	0.15, 0.60	0.0007	64%
DGE (Grade B)	4 [10,13,20,21]	29/675	35/356	0.24	0.07, 0.80	0.02	52%
DGE (Grade C)	4 [10,13,20,21]	27/675	52/356	0.28	0.16, 0.48	<0.0001	0%
Overall morbidity	5 [13,18–21]	167/458	215/443	0.61	0.47, 0.80	0.0003	3%
Intra-operative blood loss	3 [10,18,20]	651	354	−64.71	−239.94, 110.52	0.47	97%
Mortality	4 [10,12,18,20]	13/721	5/389	1.03	0.36, 2.91	0.96	0%
Pancreatic fistula	7 [10,12,13,18–21]	105/875	101/526	0.70	0.35, 1.40	0.31	69%
Bile leakage	6 [10,12,18–21]	32/851	26/506	0.61	0.34, 1.08	0.09	0%
Intra-abdominal abscess	5 [10,12,18,19,21]	83/645	38/305	0.92	0.58, 1.45	0.71	0%
Hospital stay	2 [18,20]	304	306	−1.80	−3.43, −0.18	0.03	0%

was significantly lower in Braun group (73/875) compared with Non-Braun group (116/526) (Fig. 2, OR, 0.30; 95%CI, 0.15 to 0.60; P = 0.0007). Heterogeneity existed among the pooled studies (I^2 = 64%), thus, we chose a random-effects model to lessen the analytical error. Sensitivity analyses (exclusion individual articles) reveal that the significant heterogeneity was not caused by a single study. No publication bias was shown.

Four studies [10,13,20,21] containing 1031 patients provided information on DGE grade B and grade C. The meta-analysis using a random-effects model showed a significant difference in the occurrence of DGE grade B between two groups (Fig. 3, OR, 0.24; 95%CI, 0.07 to 0.80; P = 0.02; I^2 = 52%). In terms of the incidence of DGE grade C, a fixed-effects model revealed a significantly superior outcome in the Braun group (Fig. 4, OR, 0.28; 95%CI, 0.16 to 0.48; P < 0.0001; I^2 = 0%).

3.4.2. Overall morbidity

Five of the seven included articles [13,18–21] reported overall morbidity, which was noted in 36.5% (167/458) of patients in the Braun group and in 48.5% (215/443) of those in the Non-Braun group. There was a statistically significant difference in morbidity in favor of the Braun group (OR, 0.61; 95%CI, 0.47 to 0.80; P = 0.0003; I^2 = 0%).

3.4.3. Intra-operative blood loss

Three studies [18,20,21] were analyzed for intra-operative blood loss. The random-effects model was used because of significant heterogeneity (I^2 = 97%) between these 3 studies, and the pooled effect indicated no difference between the two groups (WMD, −64.71; 95%CI, −239.94 to 110.52; p = 0.47).

3.4.4. Mortality

Four included studies [10,12,18,20] involving 1110 patients reported the mortality. The mortality of Braun group and Non-Braun group was 1.8% (13/721) and 1.3% (5/389) respectively, and the difference was not significant between the two groups (OR, 1.03; 95%CI, 0.36 to 2.91; P = 0.96; I^2 = 0%).

3.4.5. Pancreatic fistula, bile leakage and intra-abdominal abscess

Pooled analysis revealed no significant difference in the rate of pancreatic fistula (7 studies [10,12,13,18–21]: OR, 0.70; 95%CI, 0.35 to 1.40; P = 0.31; I^2 = 69%), bile leakage (6 studies [10,12,18–21]: OR, 0.61; 95%CI, 0.34 to 1.08; P = 0.09; I^2 = 0%) and intra-abdominal abscess (5 studies [10,12,18,19,21]: OR, 0.92; 95%CI, 0.58 to 1.45; P = 0.71; I^2 = 0%) between Braun group and Non-Braun group.

3.4.6. Length of hospital stay

Five studies [12,13,18,20,21] provided data on the LOS. However, only two articles [18,20] provide the standard deviation. Pooled analysis of the two articles revealed significantly shorter LOS in the Braun group than Non-Braun group (WMD, −1.80; 95%CI, −3.4 to −0.18; p = 0.03; I^2 = 0%).

3.5. Subgroup analysis

As shown in Table 4, Subgroup analysis was performed according to the two types of design in OCS: prospective OCS and retrospective OCS. The results of the subgroup analysis were similar to those when seven articles were selected except for overall morbidity. The subgroup analysis of four retrospective OCS showed no significant difference between two groups in terms of overall morbidity (p = 0.11).

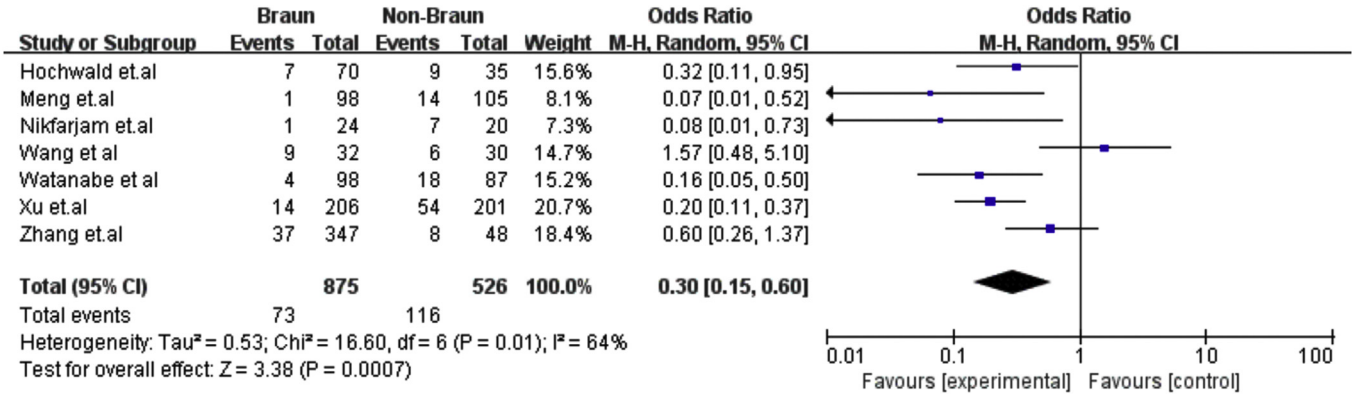

Fig. 2. Forest plot comparing DGE in Braun and Non-Braun group.

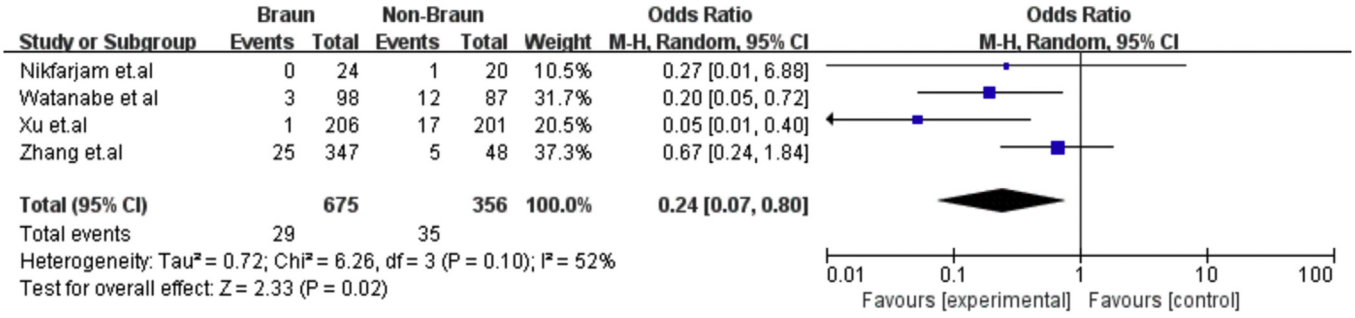

Fig. 3. Forest plot comparing DGE grade B in Braun and Non-Braun group.

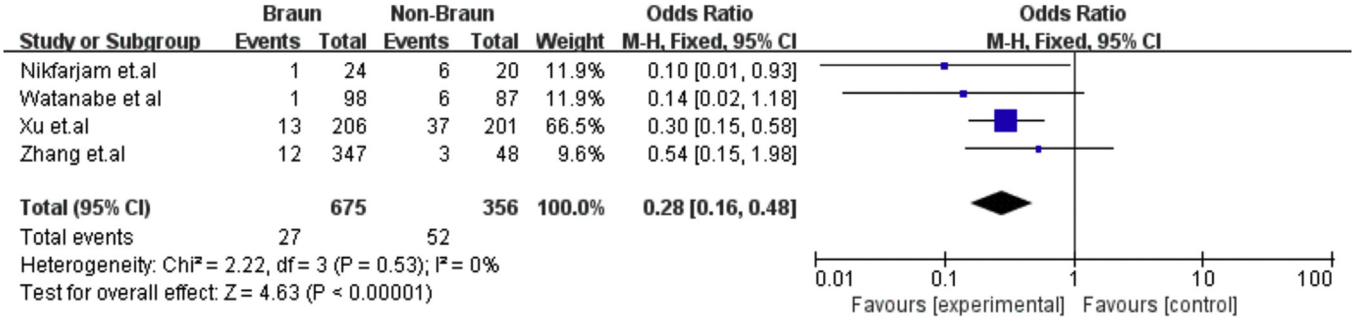

Fig. 4. Forest plot comparing DGE grade C in Braun and Non-Braun group.

Table 4
Subgroup analysis performed for studies comparing Braun and Non-Braun.

Outcomes	Studies (n)	Patients (n)		OR or WMD	95%CI	*P* value	Heterogeneity (I^2)
		Braun	Non-Braun				
Prospective OCS							
DGE	3 [12,13,18]	9/192	30/160	0.16	0.07, 0.37	<0.0001	25%
Overall morbidity	2 [13,18]	46/122	68/125	0.51	0.31, 0.85	0.01	0%
Mortality	2 [12,18]	3/168	1/140	1.68	0.23, 12.32	0.61	0%
Pancreatic fistula	3 [12,13,18]	23/192	34/160	0.55	0.20, 1.49	0.24	57%
Bile leakage	2 [12,18]	3/168	8/140	0.38	0.11, 1.34	0.13	0%
Intra-abdominal abscess	2 [12,18]	26/168	25/140	0.97	0.53, 1.80	0.93	0%
Retrospective OCS							
DGE	4 [10,19–21]	64/683	86/366	0.40	0.16, 1.02	0.05	76%
Overall morbidity	3 [19–21]	121/336	147/318	0.70	0.46, 1.09	0.11	34%
Intra-operative blood loss	2 [10,20]	553	249	−89.66	−320.77, 141.45	0.45	98%
Mortality	2 [10,20]	10/553	4/249	0.84	0.25, 2.85	0.78	0%
Pancreatic fistula	4 [10,19–21]	82/683	67/366	0.86	0.30, 2.51	0.79	80%
Bile leakage	4 [10,19–21]	29/683	18/366	0.71	0.37, 1.36	0.30	0%
Intra-abdominal abscess	3 [10,19,21]	57/477	13/165	0.85	0.43, 1.68	0.64	0%

OCS = observational clinical studies.

4. Discussion

Since Braun initially introduced the additional anastomosis 100 years ago, this additional BEE has been widely used in gastric surgery to decrease alkaline reflux gastritis (ARG) [11]. Until now, few studies have focused on the influence of BEE on the occurrence of DGE after pancreatic surgery. It seems that BEE may have other benefits more than the beneficial effect of decreasing ARG.

This meta-analysis performed here indicated that an additional BEE was related to a significant reduction in the incidence of DGE, overall morbidity and LOS. However, BEE was not superior to traditional GJ in terms of intra-operative blood loss, mortality, pancreatic fistula, bile leakage and intra-abdominal abscess. As mentioned previously, two subgroups were used to conduct the subgroup analysis, and the results were similar to those when all articles were selected, manifesting the stability of current meta-analysis.

The results of several previous studies were consistent with those derived from the present meta-analysis. In 2008, Hochwald et al. [12] found that the incidence of DGE was reduced in the presence of an additional BEE (36% Braun vs 60% no Braun, P = 0.02), and the most statistically significant difference was found in the DGE grades B and C (7% Braun vs 31% no Braun, P = 0.003). Furthermore, in a similar 2012 prospective study, Nikfarjam et al. [13] also found that the DGE rate in the Braun group was significantly lower than the standard group (4.2% vs 35.0%, P = 0.008).

Nevertheless, a lot of studies have refuted the utility of BEE in mitigating DGE. In 2014, a retrospective study [10] involving 395

patients showed no significant difference in the rate of DGE between two groups (10.7% Braun vs. 16.7% no Braun, P = 0.22). Researchers just noted that patients undergoing PD with BEE had lower occurrence of postoperative vomiting than those undergoing PD without BEE (33.3% vs 15.3%, P = 0.02). This finding seems to contradict with that derived from the current meta-analysis. In Zhang's study [10], researchers chose a longer retention of the NGT for patients. Therefore, variability in time of removing NGT may explain the diversity of the final results.

First described by Warshaw et al in 1985, the leading cause of morbidity after pancreatic surgery is DGE occurring in about half of all cases [12]. However, the pathogenesis of DGE remains controversial and has not been fully explained. The following factors have been postulated to be associated with the occurrence of DGE: (1) gastric atony as a result of reduced levels of motilin [23], (2) anastomotic stenosis or edema [24], (3) angulation or torsion of the digestive tract reconstruction [25], (4) preoperative diabetes [26], (5) postoperative complications, such as pancreatic leaks, bile leakage and intra-abdominal abscess [27], (6) gastric mucosal irritation due to bile reflux [11], and so on. It is for the last point that an addition of BEE may have the most advantageous effect. As mentioned earlier, this additional anastomosis can divert bile from the afferent limb, resulting in the reduction of bile reflux into the stomach.

As noted previously, Braun [10] introduced this modified technique of GJ. Briefly, the afferent and efferent limbs of jejunum were brought together and anastomosed using a 60-mm linear cutter stapler, and this enteroenterostomy was created 25 cm distal to the gastroenterostomy [12]. It is worth mentioning that few researchers had made some changes of this surgical procedure. In Wang's report [19], an enteroenterostomy was performed proximal to the gastroenterostomy, and the ambilateral jejunum were anastomosed using a 75-mm linear cutter stapler. Interestingly, this kind of modified BEE showed significant advantages over Non-Braun group in terms of ARG and related sequela, while no significant differences exist between the two groups in terms of DGE (28.1% BEE vs 20% Non-Braun, P = 0.455). Therefore, further appropriate trials focusing on the length of jejunal loop between enteroenterostomy and gastroenterostomy in the surgical procedure are urgently needed.

It remains controversial whether BEE can reduce the probability of marginal ulcers (MU) and pancreatic fistula. It was reported that BEE not only decreased the occurrence of ARG and MU [19], but also reduced the pressure of the biliopancreatic limb, contributing to a lower incidence of pancreatic fistula [20]. However, In Hochwald's [12] study, one patient who underwent a BEE presented with a perforation at the GJ 12 months after PD, and they speculated that the development of MU was associated with the accumulation of gastric acid which was not neutralized by alkaline bile in the jejunum near the GJ. In addition, the present study has not shown significantly lower rate of pancreatic fistula in the Braun group. Therefore, further researches are required to draw a consistent conclusion.

The current study has several limitations, and it is necessary to interpret the results with caution. First, due to the absence of RCTs focusing on this issue, only seven OCS with a small number of participants were included. This implies that present evidence is not reliable enough to guide clinical decision. Second, there was evidence of heterogeneity among the pooled studies, which may due to the differences in the reconstruction of digestive tract, anastomotic technique, surgical experience and postoperative management. Third, Most of the included studies focus on the near-term complications of PD, the lack of pooled analysis on long-term outcomes may influence the reliability of the final results.

5. Conclusions

A comprehensive review of the significance of an additional BEE was conducted in this study. The evidence from the pooled analysis of included studies suggests that the additional BEE plays an important role in reducing the incidence of DGE, overall morbidity and LOS. However, further high quality RCTs comparing BEE with traditional GJ are required to confirm this finding, and to provide a sufficiently reliable evidence for making clinical decision.

Ethical approval

Not needed.

Sources of funding

None.

Author contribution

B.-L.T. was responsible for conception and design. M.-Q.H., M.L. and J.-Y.M. participated in data collection, analysis and interpretation. M.-Q.H. and M.L. wrote the manuscript. J.-Y.M. and B.-L.T. edited and revised the manuscript.

Conflict of interest

All authors have no conflict of interests related to this article.

Guarantor

B.-L.T. is the guarantor.

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