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Review Article

The utility of Braun Enteroenterostomy with pancreaticoduodenectomy: Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Introduction: Delayed Gastric Emptying (DGE) following pancreaticoduodenectomy occurs in approximately 30% of patients, leading to longer hospital stays. Braun Enteroenterostomy (BE) is a surgical technique employed to reduce the incidence of DGE, however the current literature base is inconclusive with underpowered studies.

Methods: A systematic database search (Pubmed, Medline, Embase, Scopus and the cochrane central register of controlled trials) for randomised studies was performed using pre-specified search terms reviewing the utility of a BE with pancreaticoduodenectomy. This review was performed according to PRISMA guidelines. Included studies were assessed for bias using risk of bias 2 tool. Revman ver5.4 was used for data analysis; fixed-effects Mantel-Haenszel test was performed for dichotomous outcomes and continuous data was analysed using the Inverse Variance method.

Results: Five studies were considered suitable for inclusion for meta-analysis, resulting in a total of 407 participants, of which 178 received a BE. BE was associated with a reduction in DGE (odds ratio 0.51; 95% confidence interval 0.30-0.87, p=0.01), however no difference was seen with grade B/C DGE, post-operative pancreatic fistula and length of stay. Three studies were considered high risk of bias, and there was variability in surgical technique.

Conclusion: Meta-analysis suggests inclusion of BE may lead to a reduction in the incidence of DGE, however methodological weaknesses in available literature necessitates the need for further robust studies.

Keywords: Pancreaticoduodenectomy; Braun; Delayed gastric emptying

INTRODUCTION

A better understanding of perioperative care and decision making in patients having pancreatic surgery has led to concerted improvements in outcomes for these patients [1,2]. Centralisation in higher volume centres, better patient selection and improved surgical techniques have contributed to the mortality rate after pancreaticoduodenectomy falling well below five percent [1,3,4]. However, morbidity after this procedure is common, largely driven by the occurrence of Post-Operative Pancreatic Fistula (POPF) and Delayed Gastric Emptying (DGE) [5].

DGE occurs with a rate of up to 30% post-operatively [6]. It is characterised by the inability to tolerate an oral diet, abdominal discomfort and persistent nausea or vomiting. It is a major contributor to a prolonged hospital stay and delays in commencing adjuvant therapy, thus potentially impacting long term survival [7]. The development of postoperative DGE is inherent to pancreaticoduodenectomy with duodenal resection and loss of the duodenal pacemaker, falling levels of circulating motilin and the effects of devascularisation and denervation from extensive lymphadenectomy in cancer surgery [8]. The incidence and severity of DGE increases with the development of complications such as POPF, bile leak or intra-abdominal abscess [9]. These ideas have led to some authors further classifying DGE as primary or secondary; primary where there has been no antecedent factor, whereas secondary being where DGE has been associated with another perioperative complication [10].

Variations in surgical technique are common in pancreaticoduodenectomy with regards to pylorus preservation, gastrointestinal reconstruction and more recently inclusion of a Braun Enteroenterostomy (BE). BE involves an additional anastomosis between the afferent and efferent limbs of a gastrojejunostomy during the gastrointestinal reconstruction and it has been postulated to prevent DGE in several ways. Firstly, it

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has been demonstrated that this additional anastomosis reduces the clinical impact of bile reflux by allowing biliary and pancreatic secretions to bypass the stomach [11,12]. Furthermore, any gastric contents that enter the afferent limb of the gastrojejunostomy can enter the distal small bowel through the BE without refluxing back into the stomach. The BE also provides traction on to the limbs of the gastrojejunostomy, preventing any angulation (and occlusion) of the efferent limb [13]. Lastly, it has been suggested that BE may facilitate drainage from the biliopancreatic (afferent) limb, resulting in lower POPF rates and therefore less DGE [14].

Despite these purported benefits, the literature surrounding BE is both variable and limited. Zhou, et al., published a meta-analysis looking at BE, however 90% of their patient data coming from non-randomised studies. In their meta-analysis, BE reduced the incidence of DGE (odds ratio 0.32; 95% confidence interval 0.24-0.43, p<0.001) [15]. Since their publication, two additional randomised studies have been published, which has allowed sufficient expansion of the literature base to perform meta-analysis using only randomised data [14,16].

The objective of this meta-analysis is to use randomised data only to determine if patients undergoing pancreaticoduodenectomy, would BE reduce the incidence of DGE compared to the control groups receiving standard reconstruction. Secondary outcomes included incidence in grade B/C DGE, POPF and hospital length of stay.

MATERIAL AND METHODS

This study was conducted in accordance with PRISMA 2020 guidelines, and was registered on Prospero (Study ID: CRD42023381568) [17]. The research question in PICO format was:

In those patients undergoing pancreaticoduodenectomy (population), does introducing a Braun Enteroenterostomy (BE) in the gastrointestinal reconstruction (intervention), compared with usual reconstruction (control), reduce the rate of delayed gastric emptying (outcome)?

Criteria for considering studies for this review

All randomised controlled trials comparing BE and non-BE in the setting of pancreaticoduodenectomy were included. Observational studies, case reports and series, systematic reviews, abstracts and letters were excluded. Studies reviewing the utility of BE in other clinical situations (such as palliative bypass, following gastrectomy or bariatric surgery) along with those comparing BE with Roux-en-Y reconstructions were excluded. Only papers published in English were considered for inclusion.

Search strategy

Pubmed, Medline, Embase, Scopus and the cochrane central register of controlled trials were systematically searched using a combination of medical subject headings and key words. The search terms included:

- 'Braun enteroenterostomy or braun anastomosis or braun jejunojejunostomy' and
- 'Pancreaticoduodenectomy or pancreatoduodenectomy or Whipple or Whipples or pancreatectomy or pancreatic surgery'

No limitations were placed on the date of publication. The first search was done in March 2022 and updated in June 2024. The reference lists of identified studies, previous reviews and systematic reviews were hand-searched for additional relevant articles.

Data collection

Two authors (SG, AC) reviewed the titles and abstracts independently using covidence systematic review software (https://www.covidence.org) throughout the process. When there was disagreement, a third senior author was consulted (DB). Full text papers were obtained for all studies that could not be excluded based on title and abstract. Original authors were contacted when further information was required to clarify study details. Studies were assessed for bias using cochrane's Risk of Bias 2 (RoB 2) tool, and both reviewers independently applied the tool to each study [18]. Both SG and AC extracted data from the included studies using a predefined proforma. Data were collected regarding the study year, baseline characteristics, study methodology, criteria used to define DGE and POPF, operative techniques, along with the required information to complete the RoB 2 assessment.

Outcome measures

The primary outcome measure was the overall incidence of DGE. Secondary outcome measures included the rate of Grade B/C DGE, rate of POPF (excluding grade A POPF, as this has been re-defined as biochemical leak and not a true pancreatic fistula) and hospital Length of Stay (LOS) [19]. Historically there has been some variability in the definitions of DGE and POPF so these were defined in this review using the International Study Group of Pancreatic Surgery (ISGPS) consensus definitions, and studies were reviewed to determine if DGE and POPF were defined and graded using these classifications [8,19]. Risk of bias assessments were based on the primary outcome of the rate of DGE.

Statistical methods

Meta-analysis was performed using Review Manager (RevMan) version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A fixed-effects Mantel-Haenszel test was performed for dichotomous outcomes using the Odds Ratios (OR) with 95% Confidence Intervals (CI). Continuous data were reported as means and standard deviations and were analysed using the inverse variance method. When standard deviations were not provided, this was estimated by dividing the range by four, under the assumption that the continuous variable was normally distributed with the upper and lower limits of the range representing a deviation of two standard deviations from the mean. Statistical heterogeneity across studies was assessed by visual inspection of the forest plot and also indicated with I2 values, where a threshold of 50% indicated moderate heterogeneity, and a threshold of 75% indicated substantial heterogeneity.

RESULTS

After duplicates were removed, 107 studies were assessed for inclusion, of which only five met inclusion criteria are shown in Figure 1 and involved a total of 407 participants, 178 of which received a BE. The characteristics of the five included studies are shown in Table 1. All studies were single institution and were conducted in Iran, South Korea, Japan and India. Participants were recruited between 2011 and 2016 [14,16,20-22].

Baseline characteristics of the study participants were similar between the BE and no-BE groups are shown in Table 2. Mean ages ranged from 55 to 70 in the BE groups and 53 to 72 in the

non-BE groups. There were no-sex based differences between the BE and no-BE groups, with the majority of the participants being male. Pre-operative diabetes status was no different in the BE and no-BE groups.

Table 3 outlines the surgical techniques employed in the various studies. The extent of gastric resection varied between studies, which included classical Whipple (i.e. resection including distal gastrectomy); subtotal stomach preserving (pylorus resecting with antrum preservation) and pylorus preserving approaches. All studies involved antecolic gastrojejunostomy (or duodenojejunostomy in the case of pylorus preservation). Kakaei, et al., described blinding study investigators post procedure; but no studies reported blinding study participants [20]. Tanaka, et al., also included laparoscopic procedures [16].

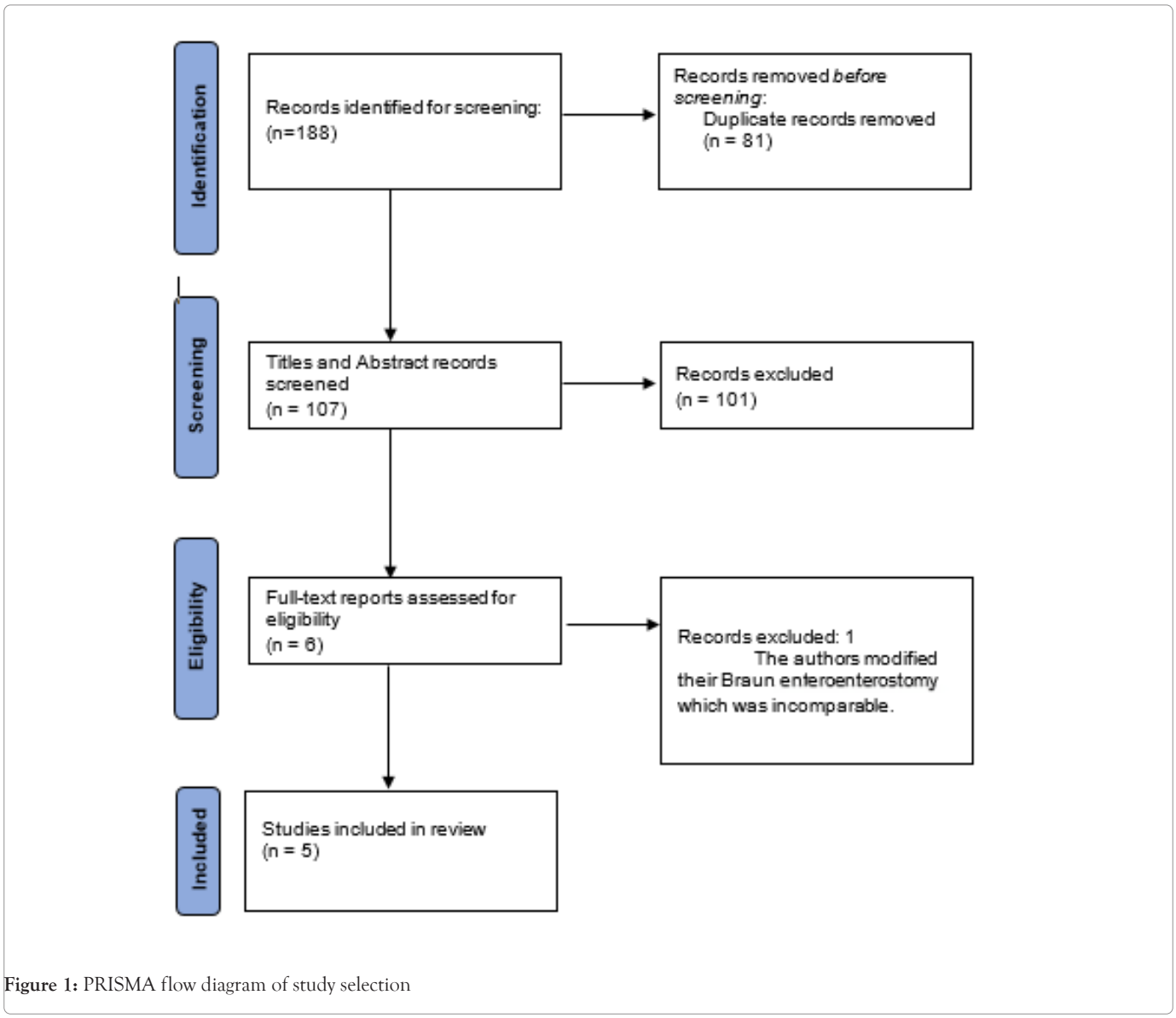

Figure 1: PRISMA flow diagram of study selection

Table 1: Characteristics of included studies for meta-analysis

	Country	Period of patient recruitment	Inclusion and exclusion criteria	Randomisation	Blinding
Kakaei 2015[16]	Iran	June to December 2013	Inclusion Patients aged 18-75 years Confirmed operable pancreatic head, duodenal or common bile duct tumours who were scheduled to have a whipple procedurel Exclusion Previous upper abdominal surgery Preoperative signs of inoperability according to imaging studies General conditions not suitable resection	Sealed envelope given to surgeon, only unopened after complete resection of the pancreaticoduodenal complex	Patient No information of patient blinding Investigator Post-operative data collected by team member who was blinded to the treatment allocation

Hwang 2016[17]	South Korea	February 2013 to June 2014	Inclusion Patients aged 20-80 years Performance status with a karnofsky score of at least 70% or ECOG grades 0 and 1 Periampullary tumours Exclusion Laparoscopic procedure Procedure more extensive that pylorus preserving PD Previous transabdominal surgery	Intraoperative randomisation to Braun or no-Braun, using computer generated random number patterns, performed right after the specimen was removed and just before reconstruction	No information on blinding
Fujieda 2017[18]	Japan	August 2011 to February 2016	Inclusion All patients scheduled to undergo PD irrespective of underlying pathology Exclusion Aged under 20 years Patients with severe co-morbidities (not further defined) Patients who declined to participate	Done intra-operatively when an operating surgeon decided the case was possible to resect	No information on blinding
Vutukuru 2017[10]	India	June 2012 to July 2016	Exclusion Previous gastric or small bowel surgery Adjacent organ resection Vascular resection/reconstruction	Patients randomised after resection by sealed enveloped technique	No information on blinding
Tanaka 2022[12]	Japan	August 2010 to November 2015	Inclusion Patients with pancreatic, bile duct, gallbladder cancers, IPMN, vater papillary pancreatic neuroendocrine, serous cystic and metastatic pancreatic tumours No exclusions made on the type of resection (pylorus preservation or resections were both included) Exclusion Cases with other organ complications	No information on randomisation technique	No information on blinding

Table 2: Baseline Characteristics of the study populations in each arm (Braun or No-Braun) of included studies

Study population (number)		Age ± standard deviation (years)			Male, number (percentage)			Pre-operative BMI			Pre-operative diabetes, number (percentage)		
Braun	**No-braun**	**Braun**	**No-braun**	**p-value**	**Braun**	**No-braun**	**p-value**	**Braun**	**No-braun**	**p-value**	**Braun**	**No-braun**	**p-value**
15	15	57.3 ± 13.8	55.3 ± 13.2	0.82	10 (66.7)	10 (66.7)	N/A	2 patients greater than 25	2 patients greater than 25	N/A	Not provided	Not provided	N/A
30	30	69 ± 8	63 ± 9	0.005	19 (63.3)	19 (63.3)	1	Not provided	Not provided	N/A	13 (43.3%)	10 (33.3)	0.426
34	34	66 (range 55-78)	72 (range 45-83)	0.16	20 (58.8)	24 (70.6)	0.31	21.3	21	0.348	6 (17.6%)	12 (35.3%)	0.168
48	56	55.2 ± 9.9	52.6 ± 10.3	0.36	28 (58.3)	36 (64.3)	0.78	Not provided	Not provided	N/A	18 (37.5%)	24 (42.8%)	0.76
51	94	70 (range 31-87)	70 (range 40-85	0.55	32 (62.7)	55 (58.5)	0.72	Not provided	Not provided	N/A	Not provided	Not provided	N/A

Table 3: Notes on the used operative technique of included studies

	Level of stomach resection	Position of gastro-jejunostomy	Position of braun enteroen-terostomy	Size of braun enteroenterostomy	Type of pancreatic anastomosis	Vascular reconstr-uction	Feeding jejunostomy
Kakaei 2015[16]	Classical whipple	Antecolic	45 cm from gastrojejunostomy	No information	pancreaticojejunostomy, duct-to-mucosa	No information	No
Hwang 2016[17]	Pylorus-preserving	Antecolic (duodeno-jejunostomy)	30 cm from duodenojejunostomy	No information	pancreaticojejunostomy, duct-to-mucosa, internal stent	Excluded	No
Fujieda 2017[18]	Subtotal stomach preserving	Antecolic	20 cm from gastrojejunostomy	3 cm	Pancreaticojejunostomy, 63:5 ratio of duct-to-mucosa:Invagination	12 patients with portal vein resection	Yes
Vutukuru 2017[10]	Likely standard whipple, but not explicitly stated	Antecolic	25 cm from gastrojejunostomy	4 cm	pancreaticojejunostomy, duct-to-mucosa, stented if duct diameter less than 3 mm	Excluded	Yes
Tanaka 2022[12]	Whipple, subtotal stomach preserving, pylorus preserving approaches all included	Antecolic	No information	No information	Pancreaticojejunostomy, duct-to-mucosa	No information	No

The randomised study from Wang, et al., was excluded due to variance in surgical technique [23]. The author's version of BE directly communicated with the stomach without separation of the limbs, so was considered non-comparable to the other studies.

Risk of bias

Risk of bias assessments using the RoB 2 tool showed one study was 'low' risk of bias, one had 'some' risk of bias and there was 'high' risk for bias in the remaining three studies are shown in Table 4. Kakaei, et al., demonstrated high risk for bias as the accepted DGE definition developed in 2007 by the ISGPS was not used, although the study had recruited in participants in 2013 and published their results in 2015 [20]. Vutukuru, et al., was considered high risk of bias as the data presented in the study's abstract did not match the data within their main text [14]. Tanaka, et al., was considered high risk of as the publication did not describe any details of the randomisation method used [16].

Delayed Gastric Emptying (DGE)

Four studies used the ISGPS definition for DGE, however Kakaei, et al., defined DGE as gastric stasis requiring nasogastric intubation for 10 days or more, or the inability to tolerate diet 14 days after the operation [20]. Fujieda, et al., only presented data for grade B/C DGE [22]. The publication of Vutukuru, et al., had varying data between the published abstract and full text, without clarification for the difference [14]. Using Vutukuru, et al's., main text data for meta-analysis, BE was associated with a reduction in DGE (odds ratio 0.51; 95% confidence interval 0.30-0.87; p=0.01, I2=0%) shown as a forest plot are shown in Figure 2A. Four studies provided data on grade B/C DGE [14,21,22]. There was no reduction in grade B/C DGE associated with BE (odds ratio 0.57; 95% confidence interval 0.28-1.20; p=0.14; I2=0%) (Figure 2B).

Table 4: Risk of bias assessments for the included studies, performed using the risk of bias 2 tool from cochrane

	Domain 1: Risk of bias arising from the randomisation process	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 3: Missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall risk of bias
Kakaei 2015[16]	Low	Low	Low	High	Low	High
Hwang 2016[17]	Low	Low	Low	Low	Low	Low
Fujieda 2017[18]	Some	Low	Low	Low	Low	Some
Vutukuru 2017[10]	Low	Low	Low	Low	High	High
Tanaka 2022[12]	High	Low	Low	Low	Low	High

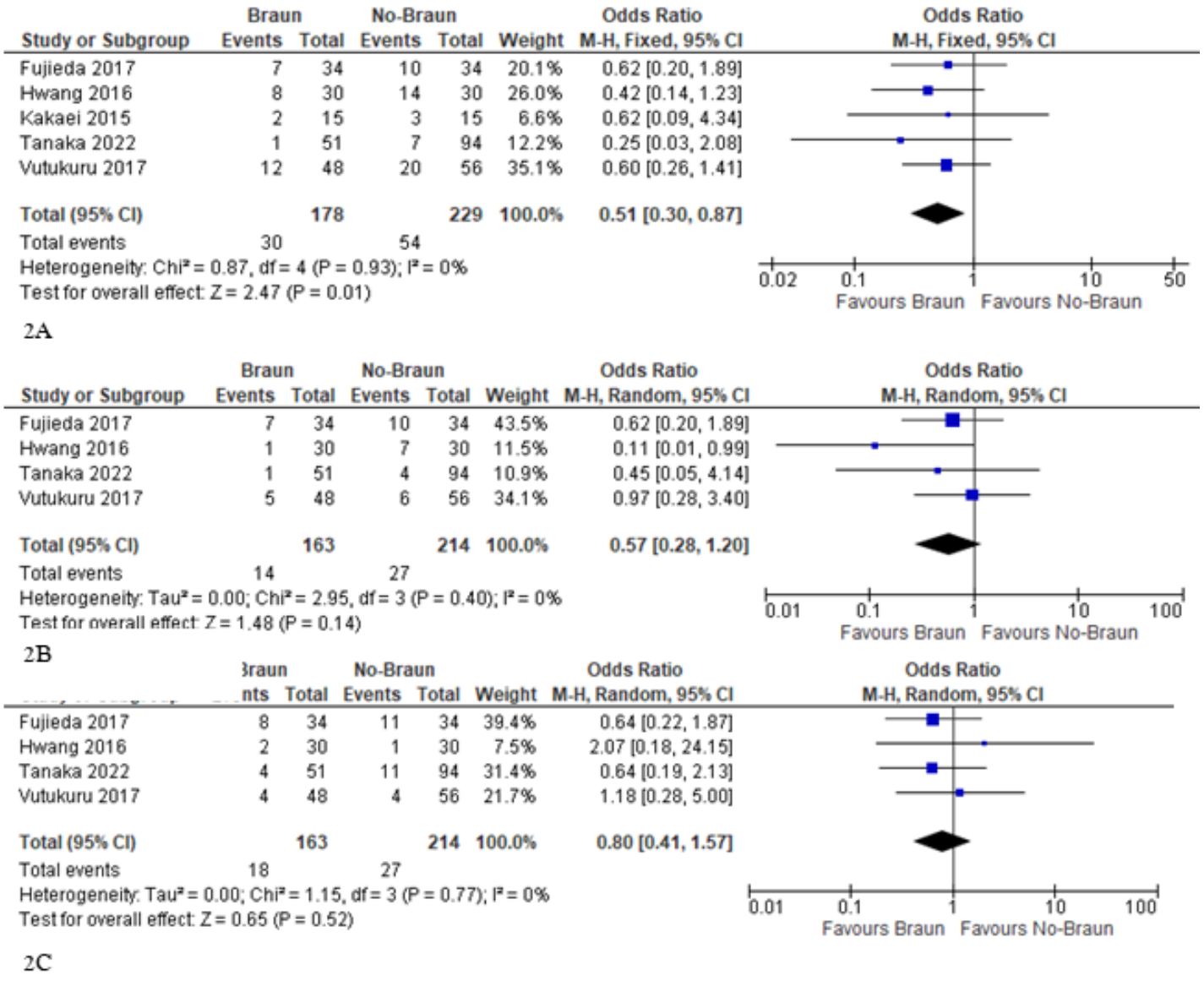

Figure 2: Forrest plots showing the relationship of braun enteroenterostomy with; A) DGE; B) Grade B/C DGE; C) Post-operative pancreatic fistula

Post-Operative Pancreatic Fistula (POPF)

Four studies provided information regarding POPF, with one study using the term 'pancreatic anastomosis leakage' without a definition or qualification, and so the data from this fifth study was not included for meta-analysis on POPF [14,16,20-22]. No difference was observed between the BE and no-BE groups (odds ratio 0.80, 95% confidence interval 0.41-1.57; p=0.52; I2=0%) (Figure 2C).

Length of hospital stay

Four studies provided data regarding length of hospital stay post procedure [14,16,21,22]. The mean length of stay for the BE and non-BE groups were was 19.6 and 21.3 day respectively. This difference was not statistically significant (p=0.31; I2=0%).

DISCUSSION

This meta-analysis, using only published randomised data showed an almost 50% reduction in the incidence of Delayed Gastric Emptying (DGE) associated with a Braun Enteroenterostomy (BE). Zhou, et al., had previously shown a higher size of effect with their meta-analysis, however their study comprised a significant proportion of observational data [15]. Of the 1604 patients including in their analysis, only 158 came from randomised studies (9.9%). Furthermore, there have been two randomised studies that have since been published which have had considerably larger sample sizes than the previous. Hence the data analysed in our meta-analysis is more robust, accepting the high risks of bias in the utilised randomised controlled trials. We did not include randomised data from Dikmen, et al., as that data was only published in abstract form [24].

Enhanced Recovery After Surgery (ERAS) protocols with pancreaticoduodenectomy have been associated with better post-operative outcomes [25]. However utilisation/implementation remains inconsistent, and many surgeons are still resistant for their routine application for all patients. Enhanced recovery with

pancreaticoduodenectomy is dependent on the avoidance of DGE as this allows early introduction of post-operative diet, reduced postoperative nausea/vomiting, less postoperative abdominal discomfort; reduced reliance on nasogastric decompression and less need for parenteral nutrition. A recent meta-analysis from Ammar, et al., showed that routine nasogastric decompression after Pancreaticoduodenectomy (PD) was associated with high rates of clinically relevant complications (defined as clavien-dindo ≥ 2) along with a longer length of stay [26]. The results of our meta-analysis supports the incorporation of BE increasing the likelihood of patients commencing early oral nutrition and avoiding prophylactic nasogastric decompression.

When limited only to grade B/C DGE, the addition of a BE in this meta-analysis did not result in a statistically significant difference. It is possible that the lack of significance is a result of underpowered trials, as grade B/C DGE occur with lower incidence, which is a limitation of small sample sizes. Furthermore, severe DGE is driven by the development of other major surgical complications such as POPF, intra-abdominal collections and bile leak. The addition of a BE in this situation has not been demonstrated to be reduce DGE. The improvements in DGE with BE are likely through reducing the grade A DGE, which may facilitate adherence to an ERAS pathway, allowing for earlier commencement and tolerance of full oral nutrition.

No difference was seen in length of stay. In these studies, a median LOS was almost 20 days, which may reflect the included studies being done in clinical settings without ERAS protocols. LOS is influenced by a variety of factors including post-operative pain, mobility, other complications, as well as societal factors. Hwang, et al., noted that in their study on South Korean patients, their length of stay was longer than studies performed in the United States or Europe [21]. The authors proposed that this difference may relate to healthcare costs and insurance systems between different countries, as well as cultural differences. All five studies in our meta-analysis came from different healthcare systems across Asia, and no comment was made in any study about presence of an ERAS protocol. Nevertheless, as DGE is associated in increasing LOS, the utility of BE to reduce postoperative stay in future studies will be of ongoing interest [25,27].

None of the studies reported any complications associated with a BE. The theoretical risk of an additional leak or bleed from an extra anastomosis has not been demonstrated in the data. A BE can be considered safe.

The five included studies had variation is surgical technique, reflecting that the studies were done in different health systems. Heterogeneity in operative technique is a common challenge in surgical research, which is commonly seen with pancreaticoduodenectomy. Considering the small sample number of studies, it was not possible for subgroup analyses to determine if BE is superior with certain variations. Varghese, et al., performed a network meta-analysis in an attempt to compare all resections and reconstructions in pancreaticoduodenectomy, with results suggesting that pylorus resecting antecolic billroth II with BE seemed to be associated with the lowest rates of DGE, results consistent with our meta-analysis [4,28].

Despite this meta-analysis of only randomised studies finding a statistically significant difference, methodological and reporting concerns do weaken the generalisability of the results. Each trial was underpowered, with limited blinding and three studies were deemed at high risk of bias. Nevertheless, our results show promise with BE and this meta-analysis should provide basis for a large high quality randomised controlled trial on Braun Enteroenterostomy.

CONCLUSION

This meta-analysis on randomised data shows that Braun enteroenterostomy is associated with a reduced incidence of delayed gastric emptying facilitating enhanced recovery. The methodological weaknesses in the available studies necessitates the need for further robust studies examining the technique of BE for pancreaticoduodenectomy.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

STATEMENT OF ETHICS

As this study was a meta-analysis on already published data, ethical approval was not required.

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The study was funded locally through Hunter Surgical Clinical Research Unit. The funder had no role in the design, data collection, data analysis, and reporting of this study.

AUTHOR CONTRIBUTIONS

Saksham Gupta (SG) contributed to the design, analysis, and write-up of the manuscript.

Andrea Cross (AC) contributed to the design and analysis of the manuscript.

David Burnett (DB) contributed to the design, analysis, and review of the manuscript.

Steve Smith (SS) contributed to the design and review of the manuscript.

DATA AVAILABITY STATEMENT

No new data were created or analysed in this study. The original papers used to gather data to perform this meta-analysis are publicly available on PubMed or can be requested from the corresponding author, Saksham Gupta (saksham_gupta@live.com.au).

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