International Journal of Medical Science and Clinical Invention 5(12): 4210-4219, 2018
DOI:10.18535/ijmsci/v5i12.03 **ICV 2016: 77.2**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article

Endoscopic or minimally invasive surgical approach for infected necrotizing pancreatitis: a systematic review and meta-analysis.

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Abstract:
Background and Aim: The incidence of acute pancreatitis is rising around the world, thus further increasing the burden on healthcare services. Approximately 10% of patients with acute pancreatitis will develop infected necrotizing pancreatitis, which is the leading cause of high mortality in the late phase. There is currently no consensus with regard to the use of endoscopic or minimally invasive surgical as the first-line therapy of choice for infected necrotizing pancreatitis. However, more clinical research regarding the superiority of the endoscopic approach has been published recently. Therefore, we conducted a systematic review and meta-analysis to determine which of the two treatments leads to a better prognosis.
Methods: Four databases (Medline, SinoMed, EMBASE, and Cochrane Library) were searched for eligible studies from 1980 to 2018 comparing endoscopic and minimally invasive surgical for infected necrotizing pancreatitis.
Results: Two RCTs and seven clinical cohort studies were included. After the analysis of data amenable to polling, significant advantages were found in favor of the endoscopic approach in terms of pancreatic fistula (OR=0.10, 95%CI 0.04–0.30, P<0.001)and length of hospital stay (WMD=–24.72, 95%CI=–33.87 to –15.57, P<0.001). No marked differences were found in terms of mortality, multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, recurrence of pseudocysts, length of stay in the ICU, endocrine insufficiency and exocrine insufficiency.
Conclusion: Compared with minimally invasive surgical, endoscopic remedy evidently improved short-term outcomes for infected necrotizing pancreatitis, including pancreatic fistula and length of hospital stay. Furthermore, relevant multicenter RCTs are eager to prove these findings.

Keywords: endoscopic; infected necrotizing pancreatitis; meta-analysis; surgery; treatment outcome

Introduction

Acute pancreatitis (AP), one of the most common gastrointestinal diseases worldwide (1), is an inflammatory disease initiated by intra-acinar activation of proteolysis pancreatic enzymes, which causes a source of substantial service burden and hospital cost in nearly all countries (2). The 2012 revised Atlanta classification divides AP into three clinical severity levels of mild, moderate and severe (3). More than half of patients with AP will develop edematous pancreatitis with a mild course, which is a self-limiting disease that resolves with conservative medical management, requiring only a brief period of hospitalization (4). Moderate severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP), often accompanied by necrosis of the (peri) pancreatic tissue or (multiple) organ failure (MOF), is still a challenge in the medical field, even with the ever-progressing level of medical treatment (5). Currently, there is no clear indicator of the development of severe pancreatitis. Gallstones and alcohol abuse are the main prevalent causes of AP. In addition, hyperlipidemia, hyperkalemia, anatomic variation and idiopathic acute pancreatitis (IAP) act as other indispensable factors for AP (6). With the development of auxiliary examinations such as EUS, MRCP and CT, most incidences of IAP possess definitive etiology and could prevent recurrence of pancreatitis (7). Implementation of cholecystectomy or endoscopic sphincterotomy effectively prevents the incidence of recurrent biliary pancreatitis (8). The clinical course of AP can be divided into 2 phases. In the first phase, systemic inflammatory response syndrome (SIRS) and MOF occur frequently and are the main cause of death. The late phase is characterized by local complications of necrosis and pancreatic fluid collections (9), which contain peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected). Approximately 33% of patients with walled-off pancreatic necrosis (WON) and acute necrotizing pancreatitis (ANP) are often associated with infection (10) leading to bowel obstruction, bowel fistulisation, haemorrhage, prolonged hospitalization and even death (11). Early fluid resuscitation, enteral nutrition, antibiotics and intervention are of vital importance to treat INP (12). Surgical resection of necrosis is an essential therapy for the INP, which should be performed at least four weeks after the onset of pancreatitis. Traditionally, these fluid collections following INP were managed surgically with open trans-peritoneal debridement (13). This approach has a mortality rate of 11.4 to 20.3% (14). Due to the high mortality rate with open surgery, the use of endoscopic and minimally invasive techniques, such as percutaneous catheter drainage (PCD), mini incision drainage (MID), video-assisted debridement (VAD), laparoscopic transgastric drainage (LTD) and endoscopic ultrasound-guided transluminal drainage (ETD), endoscopic transgastric necrosectomy (ETG) has gained increasing popularity in many centers (15). To date, endoscopic and MIS have been recommended as the preferred treatment of INP by an increasing number of guidelines. However, it has not yet been concluded which treatment is more effective, so the meta-analysis is necessity. In this systematic review and meta-analysis, our aim is to compare the two strategies in the treatment of INP.

Methods

Ethical approval or patient consent was not required because the present study was a review of the previous published literature.

Search strategy and study selection criteria

A computerized search spanning the years 1980 to 2018 was conducted on the Medline, Sino Med, EMBASE, and Cochrane Library databases. The following search terms were used in all possible combinations: “pancreatitis”, “infected necrotizing pancreatitis”, “walled off pancreatic necrosis”, “endoscopic approach”, “endoscopic drainage”, “endoscopic necrosectomy”, “surgical step-up approach”, “minimally invasive approach”, “randomized comparative trials”, “prospective trials”, and “retrospective trials”. The detailed search strategy for each database was provided (see appendix content). The search was limited to human subjects. There was no language limitation. The titles and abstracts of potentially relevant studies identified by the computerized search were reviewed. Full-text articles were obtained for detailed evaluation, and eligible studies were included in the systematic review. The findings of NRS may also be useful to inform the design of a subsequent randomized trial. The inclusion criteria were the following: both RCTs and observational clinical trials; the study included patients who were of either sex, had a clinical diagnosis of INP; both endoscopic and MIS should be administered as the treatment, with the aim of the trial being a comparison of the endoscopic approach and MIS in treating INP; the outcomes should be clearly described including at least one of four major outcomes, such as the incidence of mortality, MOF, LOS and PF.

The exclusion criteria were the following: absence of comparison between endoscopic and MIS approaches; the characteristics of patients and information data about treatment outcome, which were insufficiently clear; and case reports.

Data collection and extraction

Two authors independently extracted data from reviewing all titles and abstracts of the searched papers. The following information was recorded from the included trials: first author, year of publication, number of participants. Basic data about gender, age, APACHE II score, and C-reactive protein (CRP, mg/L) were extracted and analyzed. To compare the clinical outcomes of the endoscopic and surgical step-up approach groups, data on mortality and MOF, intra-abdominal bleeding, PF, new-onset diabetes or impaired glucose tolerance, exocrine insufficiency, and LOS were extracted. We used a formula adopted by previous studies to acquire the mean and standard deviation (16). According to these criteria, two independent reviewers reached a consensus when discrepancies appeared and performed identification and selection of the studies. The selection process was documented according to PRISMA criteria.

Outcome measures

The short-term outcomes were the incidence of mortality, MOF, intra-abdominal bleeding, PF, length of stay in ICU, LOS and enterocutaneous fistula. The long-term outcomes were other chronic complications, such as recurrence of pseudocysts, new-onset diabetes or impaired glucose tolerance, and exocrine insufficiency.

Quality assessment and risk of bias

Two readers independently extracted and checked the data from the enrolled studies to ensure consistency. The quality of the included RCTs, as assessed by the Cochrane Handbook for Systematic Reviews of Interventions, and quality assessment of the included retrospective trials, assessed by the Newcastle–Ottawa Scale. Egger test, was used to assess publication bias, which was based on the OR of mortality in necrotizing pancreatitis.

Statistical analyses

For alignment outcomes, the number of patients for each treatment outcome was used in the analysis. Odds ratios (ORs and variances) for the 10 different complications comparing endoscopic and MIS approaches were calculated for each comparative study. The heterogeneity of all test parameters was examined with the Q-statistic test and I^2 index for sensitivity and specificity. Heterogeneity was considered to be significant if $p < 0.10$ (Q statistic) or I^2 value was 50% or more. The associated log ORs were meta-analyzed using a restricted maximum-likelihood random effects model, after which the results were transformed back into the OR metric. The random-effects model was used regardless of whether there was significant random-effects variation. Fixed effects model is performed as a sensitivity test. The study included both randomized clinical trials and observational studies, and we conducted subgroup analyses according to the study characteristics (RCT or not) in order to analyze sources of heterogeneity. All statistical analyses were conducted using STATA 14.0. For dichotomous outcomes in the extracted data, OR and 95%CI were calculated, and WMD (Weighted Mean Difference) were used for continuous outcomes. When the interquartile range and median were given instead of the standard deviation (SD), we converted the data using the Hozo algorithm to estimate the standard deviation. We performed sensitivity analysis to assess the stability of the results and investigate the influence of each study by omitting a single study sequentially. Publication bias was shown by funnel plot.

Results

Included trial characteristics and quality assessment

The initial 1563 citations were identified based on a study of the subject and a summary of the literature, of which 784 articles were thereafter excluded because of duplication. After reviewing the title and abstract of the remaining 53 studies, only 14 full-text studies were evaluated for further assessment, and five records were excluded due to incomplete data. Eventually, 9 clinical studies were consistent with the inclusion requirements (17-25). A detailed study flow-diagram is shown in Fig. 1.

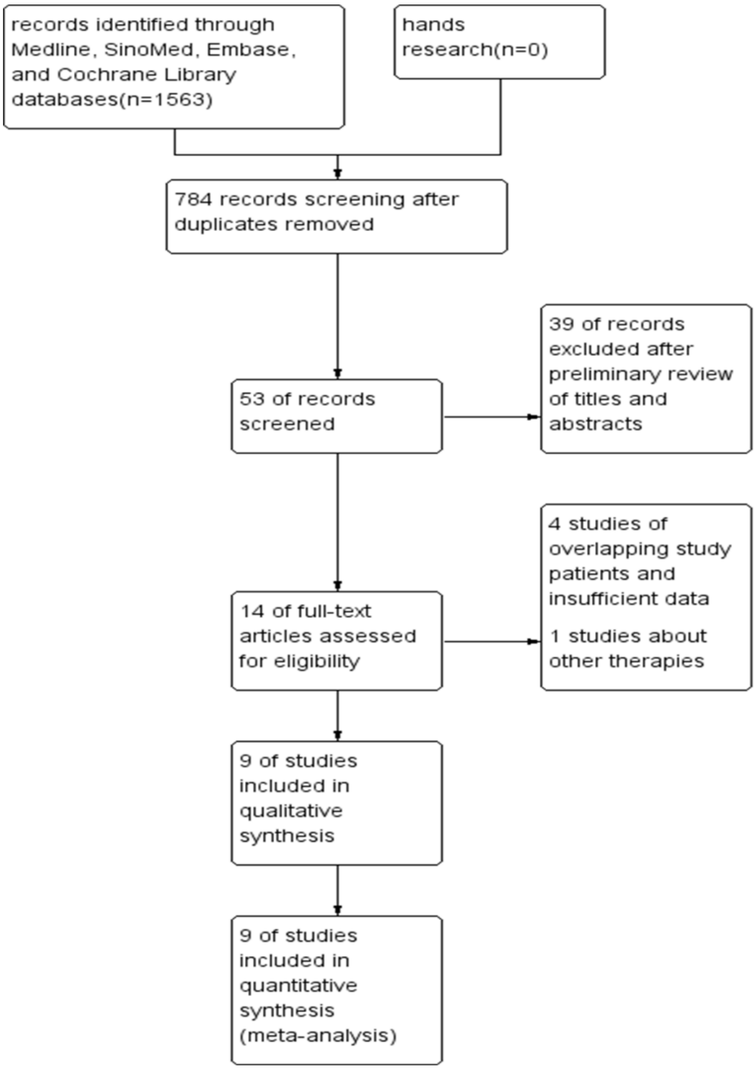

Figure 1. Flow diagram for selection of studies for included in this meta-analysis.

The characteristics of the included studies are illustrated in Table 1.

Table1. Main characteristics of the included studies

Author year	Study period	Country	Study design	Center	Group(E/S)	age(y)† (E/S)	Male (%) (E/S)	Pathology (%) (E/S)	intervention	ApacheII score†	CRP (mg/L)†
van Brunschot et al, 2017	Sep,20,2011-Jan,29,2015	Netherlands	RCT	multicenter	51/47	63 (14)/ 60 (11)	34 (67)/ 29(62)	Biliary 26(51)/30 (64) Alcohol 7(14) /7(15) Other‡ 18 (35)/10 (21)	endoscopic/surgical step-up	9(5-13) /10 (6-13)	168(105–258)/ 189 (136–301)
Bakker OJ et al, 2012	Aug,20,2008-Mar,3, 2010	Netherlands	RCT	multicenter	10/10	62 (58-70) /64 (46-72)	6(60)/ 8 (80)	Biliary 6 (60)/ 7 (70) Alcohol2(20)/2(20) Other‡ 2 (20)/1 (10)	endoscopic/surgical necrosectomy	10(614) /11 (7-14)	141(11-196)/ 232 (140-275)
Woo S et al,2018	Jan,1,2011-Dec,31,2016	Australian	retrospective	Single center	12/8	69 (31-81)/60(32–72)	8(67)/ 6 (75)	Biliary 8 (67)/2 (25) Alcohol 0 (0)/ 1 (12.5) Post-ERCP1(8)/ 1(12.5) Other‡3 (25)/4 (50)	Endoscopic drainage/ PCD	not reported	320(212–525)/ 222 (46–469)
He W et al, 2016	May,17,2013-Dec,6,2014	China	prospective	Single center	13/13	48 (27–55)/ 48 (43–59)	5(45.5)/ 7(53.8)	Biliary 5(45.5)/7(53.8) Alcohol 4(36.4)/ 2(15.4) Hypertriglyceridemia1(9.1)/4(30.8) Hypercalcei1(9.1)/ 0 (0)	endoscopic/ surgical step-up	7(6-10) /10 (8-14)	179 (118–258)/ 172 (106–351)
Khreiss M et al, 2015	2008-2013	USA	retrospective	Singlecenter	20/20	55(42.566)/55. 37-60.5	9 (45)/ 16 (80)	Biliary 9 (45)/13 (65) Alcohol 3 (15)/ 3 (12) Idiopathic 2 (10)/3 (15)	endoscopic/ surgical step-up	not reported	not reported
Kumar N et al, 2014	Jan,2009-Dec,2010	USA	prospective	Single center	12/12	58.9(3.9)/53.3(3.0)	8(66.7)/ 9(75)	Alcohol 3(25)/ 3(25) Biliary 7(58.3)/5(41.6) Hypertriglyceridemia0(0)/ 1(8.3) Post-ERCP 0(0)/ 1(8.3) Unknown2(16.7)/2(16.7	endoscopic/ surgical step-up	10.1(1.1)/9.4(1.2)	not reported
Tan V et al, 2014	May,2005-Sep, 2011	France	retrospective	multicenter	11/21	51(42-57)/52(47–60)	9(82)/ 14 (67)	Biliary5(45)/6(29) Alcohol4(36)/3(21.4) Other‡2 (18)/9 (43)	endoscopic/ surgical step-up	9(5-11)/12(10-16)	not reported
Bausch D et al, 2012	2002-2010	Germany	retrospective	Single center	18/14	58 (15–84)/61(20–75)	10(55.6) / 11(78.5)	Alcohol4(22.2)/3(21.4) Biliary5(27.8)/4(28.6) Unknown7(38.9)/2(14.3 PostERCP1(5.5)/2(14.3	Endoscopic/MIS/ONE	not reported	163 (3–276) / 248 (4–396)
Gluck M et al, 2010	Jan,2006-Aug,2009	USA	retrospective	Single center	23/43	59 (14)/ 54 (17	18(78)/ 25(58)	Alcohol4(17)/6(14) Biliary13(56)/24(56) Idiopathic4(17)/3 (7) PostERCP0(0)/1(2)	Endoscopic+PCD/ PCD	not reported	not reported

The quality of the included RCTs, as assessed by the Cochrane Handbook for Systematic Reviews of Interventions, is displayed in Table 2, and the quality assessment of the included retrospective trials, assessed by the Newcastle–Ottawa Scale, is summarized in Table 3.

Table 2. Quality assessment of included studies: quality of the included RCTs

Study	Adequate sequence generation	Adequate allocation concealment	Blinding	Incomplete outcome data adequately addressed	Free of selective reporting	Free of other bias
Sandra van Bru schot	Yes	Yes	No	Yes	Yes	No
Olaf J. Bakker	Yes	Yes	No	Yes	Yes	No

Table 3 Quality assessment of included studies: quality of the included prospective studies.

Ref.	Representativeness of treated arm	Selection of the comparative treatment arm (s)	Ascertainment of the treatment regimen	Demonstration that outcome of interest was not present at star of study	Comparability between patients in different treatment arms: main factor	Comparability between patients in different treatment arms:secon-dary factor	Assessment of o-utcome with independency	Adequacy of follow-up length (to assess outcome)	Lost to follow-up acceptable (less than 10% and reported)
Woo Shanan	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Wen HuaHe	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Mohammad Khreiss	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Nitin Kumar	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Virianne Tan	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Dirk Bausch	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Micheal Gluck	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes

Details of the trial process

Nine studies were selected, with a total of 358 patients (170 patients underwent the endoscopic approach and 188 patients underwent MIS) included. The two RCTs were a multi-center, randomized, superiority trial that recruited adult (≥18 years of age) patients from several university medical centers and teaching hospitals of the Dutch Pancreatitis Study Group. The two prospective cohort studies compared initial endoscopic transluminal drainage and direct endoscopic necrosectomy with the MIS method in the treatment of INP, which recorded the mortality, MOF and other complications. The other five retrospective studies reported on the different outcomes of endoscopic, minimally invasive surgery and open necrosectomy in treating INP. These studies all have a more than three-month follow-up, recording both the short-term outcomes (mortality, MOF, PF, intra-abdominal bleeding) and long-term conditions of prognosis (new-onset diabetes or impaired glucose tolerance).

Meta-analysis results

Short-term outcomes: mortality, MOF.

All nine studies (17-25) presented data on the incidence of mortality of endoscopic and MIS approaches. None of the patients died in the study by Mohmmad et al. A random effect model was applied even if there is no heterogeneity among them (I^2=0.0%, P=0.650). According to the subgroup analysis of results from the RCT and retrospective studies. There was no significant reduction in mortality on the RCT studies (OR=0.65, 95%CI 0.08–5.14, P=0.683), retrospective studies (OR=0.43, 95%CI 0.14–1.30, P=0.133) and whole studies (OR=0.68, 95%CI 0.32–1.44, P=0.310) (Fig. 2.a).

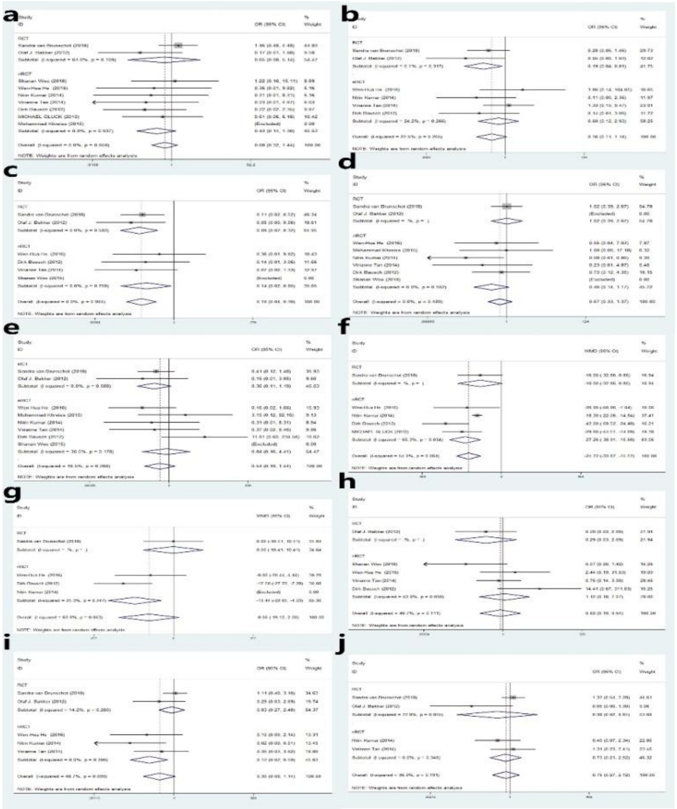

Figure 2. Forest plot of the merits between endoscopic and the minimally invasive surgical in the light of Short-term outcomes and Long-term outcomes. (a. mortality. b. multiple organ failure. c. pancreatic fistula. d. intra-abdominal bleeding. e. enterocutaneous fistula .f. Length of stay in hospital. g. Length of stay in ICU .h. recurrence of pseudocysts. i. new-onset diabetes j. Exocrine insufficiency) CI=confidence interval, OR=odds risk, WMD= Weighted Mean Difference.

Five studies (17-20, 23-24) reported the incidence of MOF. Five out of 108 (4.63%) patients in the endoscopic group and 19 out of 98 (19.39%) patients in the MIS group had an MOF during the treatment period. Random effect model was applied. there is no heterogeneity among them (I^2=22.5%, P=0.265).There were significant differences between the two groups in MOF on the RCT studies (OR=0.19, 95%CI 0.04–0.81, P=0.024), but no differences on the retrospective studies (OR=0.60, 95%CI 0.12–2.93, P=0.529) and whole studies (OR=0.36, 95%CI 0.11–1.14, P=0.082) (Fig. 2.b).

Short-term outcomes: PF, intra-abdominal bleeding, enterocutaneous fistula.

Six studies (17-19, 21, 23-24) recorded pancreatic fistulas were external (i.e., pancreaticocutaneous fistulas) with no heterogeneity being observed (I^2=0.0%, P=0.904) among them. After aggregation of the data, we found that the endoscopic approach was associated with a significant reduction in the rate of PF on the RCT studies (OR=0.09, 95%CI 0.02–0.32, P<0.001), retrospective studies (OR=0.14, 95%CI 0.02–0.85, P=0.033) and whole studies (OR=0.10, 95%CI 0.04–0.30, P<0.001) (Fig. 2.c). Eight research report the intra-abdominal bleeding (17-24) with no heterogeneity being observed (I^2=0.0%, P=0.489) among them. There was no significant reduction on the RCT studies (OR=1.02, 95%CI 0.39–2.67, P=0.972), retrospective studies (OR=0.40, 95%CI 0.14–1.17, P=0.094) and whole studies (OR=0.67, 95%CI 0.33–1.37, P=0.271) (Fig. 2.d). And eight studies about enterocutaneous fistula (17-25). There is no heterogeneity among them (I^2=18.5%, P=0.288). The RCT studies (OR=0.36, 95%CI 0.11–1.19, P=0.094), retrospective studies (OR=0.84, 95%CI 0.16–4.41, P=0.832) and whole studies (OR=0.54, 95%CI 0.19–1.54, P=0.248) (Fig. 2.e) in the endoscopic approach, the differences were not significant.

Medical resources: Length of stay in hospital, Days in intensive care.

Although all studies compared the endoscopic procedure (n=170) with the MIS procedure (n=188) with median or mean hospital stays and Days in intensive care, some studies provide median and IQR that makes analysis impossible. Six studies (17, 19-20, 23, 25) were analysis with significant heterogeneity being observed among them (I^2=54.9%, P=0.064).There were obvious differences between the two groups in LOS on the retrospective studies (WMD=–27.26, 95%CI=–38.91 to –15.60, P<0.001) and whole studies (WMD=–24.72, 95%CI=–33.87 to –15.57, P<0.001) (Fig. 2.f). The endoscopic approach group had a shorter length of hospital stay compared with the MIS group, but the Days in intensive care did not show significant advantages. Four studies (17, 19, 20, 23) record it with significant heterogeneity being observed among them (I^2=63.9%, P=0.063), the whole studies (WMD=–8.56, 95%CI=–19.12 to –2.00, P=0.112 Figs. 2.g).

Long-term outcomes: recurrence of pseudocyst.

A long-term prognosis is also a crucial criterion for determining the quality of treatment methods. A small number of patients relapsed with pancreatic cysts in all studies over 6 months of follow-up. Five studies (18-19, 21, 23, 24) were analysis with no heterogeneity among them (I^2=46.7%, P=0.111), there is no significant difference between the two treatment methods on the retrospective studies (OR=1.12, 95%CI 0.18–7.07, P=0.906) and whole studies (OR=0.82, 95%CI 0.19–3.64, P=0.797) (Fig. 2.h)..

Long-term outcomes: New-onset diabetes, exocrine insufficiency.

Five included studies (17-20, 24) provided data on endocrine insufficiency, which included 82 cases in the endoscopic approach group and 87 cases in the MIS group. Twelve out of 82 (15.85%) patients who underwent the endoscopic procedure were diagnosed with new-onset diabetes, whereas 27 out of 87 (31.03%) patients who underwent the MIS procedure were diagnosed. There is significant heterogeneity among them (I^2=48.7%, P=0.099).A pooled analysis with follow-up durations of > 3 months showed that there were no significant differences between the two groups in the induction of endocrine insufficiency on the RCT studies (OR=0.83, 95%CI 0.27–2.48, P=0.732), retrospective studies (OR=0.12, 95%CI 0.02–0.59, P=0.009) and whole studies (OR=0.30, 95%CI 0.08–1.14, P=0.077) (Fig. 2.i). Data regarding exocrine insufficiency were available in four trials (17-18, 20, 24). No heterogeneity was found among them (I^2=36.9%, P=0.191).There were no significant differences found in the induction of exocrine insufficiency between the endoscopic and MIS groups on the RCT studies (OR=0.38, 95%CI 0.02–8.64, P=0.546), retrospective studies (OR=0.73, 95%CI 0.21–2.52, P=0.622) and whole studies (OR=0.75, 95%CI 0.27–2.12, P=0.588) (Fig. 2.j).

Subgroup and Sensitivity analysis

Subgroup analyses were performed to evaluate whether the ORs of outcome measures were different among the study characteristics. There were significantly difference in MOF on the RCT studies only but no significant difference on the retrospective studies. Based on stratified analysis results of the RCT and retrospective studies, there is no difference between endoscopic and MIS. Sensitivity analysis was performed to assess the stability of pooled results. Among the seven studies, the significant results were not obviously altered after sequentially omitting each study. In the pooled results comparing the incidence of mortality, after excluding the Sandra van Brunschot, the heterogeneity decreased significantly (OR=0.719, 95%CI=0.277–1.865, P=0.497, I^2 =28%) and showed that there was no significant difference in preventing the incidence of mortality between the two groups; hence, it was regarded as a result of heterogeneity. Likewise, the other studies were considered as the source of heterogeneity because the heterogeneity significantly changed and showed that there was no significant difference in preventing the incidence of mortality between the two groups by excluding each of these studies in the pooled results comparing the incidence of mortality. A sensitivity analysis was conducted to determine whether the exclusion of this study would alter the result, and exclusion of this study from the meta-analysis did not substantially influence the results.

In this part of the study, two RCTs and five retrospective trials were included. The funnel plots of the ORs for mortality and necrotizing pancreatitis were used to assess publication bias. Egger test results showed Pr > jzj=1.00 (Fig. 3). Therefore, we believe that the risk of publication bias is low in this meta-analysis.

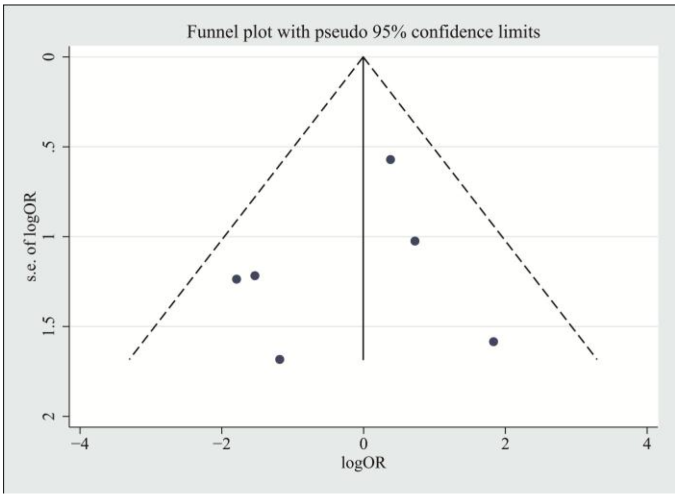

Figure 3. Funnel plot of two intervention for outcome of mortality. OR= odds risk, SE=standard error.

Discussion

Summary of the main results

With the rising incidence of INP, feasible and effective management is greatly needed (26). At present, endoscopic and MIS procedures play an important role in the treatment of INP (27). It is hard to say which is more effective. However, there have been many studies about the preponderance of endoscopic procedures recently (28-30), including the direct single use of endoscopic and the combined endoscopic and percutaneous approach. However, these documents have their own shortcomings, such as the small number of research objects and no multi-center research. Therefore, the focus of this analysis was to evaluate the efficacy of two different approaches in the treatment of INP. The meta-analysis identified seven published studies that assessed the outcomes of patients with INP who underwent the endoscopic or MIS approach. There are few published RCTs because of the lack of patients, necessary equipment, and technically savvy experts in addition to the presence of uncontrollable risk during treatment. Much evidence of effects cannot be adequately studied in randomized trials, such as long-term and rare outcomes. Therefore, we analyzed all cohort studies in this study. For the main results, there was no notable difference in mortality and MOF between the two methods in patients with infected necrosis. Improved short-term outcomes, including reduced incidence of PF and decreased LOS, were detected in patients who underwent an endoscopic approach. Regarding the outcome of new-onset diabetes and exocrine insufficiency, the endoscopic procedure reported no better outcome of exocrine insufficiency (follow-up time >2 months) when compared to patients who underwent an MIS procedure. There has been great controversy between pancreatitis and diabetes. Malka D's study in 2000 suggested that long-term development of pancreatic insufficiency was not reliant on the type of surgical procedure but instead may be related to the features of chronic pancreatitis (31). Shen HN's matched controls arrived at the conclusion that the risk of diabetes increases by twofold after INP (32).

Comparison with previous studies

In consideration of the long history of medical development and AP's widespread application, the best treatment has obviously improved. It was recognized that conservative treatment of INP was the major choice rather than surgery before the twentieth century (33). As the understanding of the disease deepens, surgical treatment (open necrosectomy) of severe pancreatitis gradually reached a consensus ten years ago. Multiple multicenter RCT and meta-analysis support this view (34, 35). In the twenty-first century, increasing evidence has proven that minimally invasive treatment is superior to open surgery (36-40). It is common for us to see many diverse minimally invasive treatments to cure INP in most hospitals. Spanning the past several years, many studies have begun to report the advantage of endoscopic procedures (41, 42). However, RCTs are still scarce. Gurusamy et al. addressed the advantage of different interventions for necrotising pancreatitis in low to very low quality evidence in 2016.but the review mainly evaluated the open necrosectomy and minimally invasive step-up approach for the treatment of necrotising pancreatitis. Luigiano et al published a review about the comparison of endoscopic versus non-endoscopic techniques. The key focus of this study is endoscopic necrosectomy rather than comparison between endoscopic and MIS. All in all, this is a novel systematic review and meta-analysis to compare endoscopic with MIS procedures for the treatment of INP. Due to the insufficiency of evidence, we present this meta-analysis by consolidating multiple studies to enable enhanced clinical decision making in the future.

Limitations of the study

However, despite a comprehensive analysis, there are also many limitations that should be taken into consideration in our meta-analysis. First, the studies included in the meta-analysis were not all RCTS. Second, in the literature-included studies, every study in the endoscopic approach is not completely similar. Weather the location of WON adjacent to the GI lumen affects the final curative effect is still unknown. Third, because of the different intervention timings, it was difficult to avoid these slight differences. Fourth, partial missing information in a few articles may lead to biased results. We have attempted to contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data. In addition to the portions of the studies that did not directly provide means and standard deviations, the author used Hozo's algorithm to estimate those values; this may have introduced bias. Moreover, clinical and method logical heterogeneities were observed in several parameters in the meta-analysis given the variation in surgical techniques, patient composition, and preferences among different centers. Finally, the assessment indices of the postoperative clinical complications were not unified, and differences existed in with each operative technique, such as operation surgical skills, incision length, and operation time, which might also affect the results. True heterogeneity and poor methodological quality could also lead to an asymmetric plot (43, 44). In the future, larger, higher quality clinical trials comparing the two approaches should be expected, and we will conduct a more detailed subgroup analysis to explore the sources of heterogeneity to obtain a more reliable conclusion.

Conclusion

In summary, there is no difference in therapeutic effect between the two methods in terms of long-term effects. But refer to the short outcomes, we demonstrated that improved short-term outcomes, including PF and LOS, were recorded in patients who underwent endoscopic approach. There is a great need for more RCTs to confirm these advantages. In addition, future studies will be required to further define the optimal time and various techniques for the endoscopic procedure.

Acknowledgement

This study was funded by Key project to tackle key problems in health industry in Tianjin 16KG159, Project of Tianjin thousands of people plan.

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