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Research Article

Comparative Assessment of Laparoscopic and Open Pancreaticoduodenectomy: A Systematic Review of Randomized Controlled Trials

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Abstract

Recently, many investigations have been approached to develop advanced, safe surgical procedures with minimally invasive surgeries (MIS) to achieve the best medical service for patients undergoing such procedures. We aim to conduct a systematic review that summarizes the results of all published RCTs that were originally developed to compare laparoscopic pancreatoduodenectomy (LPD) and open pancreatoduodenectomy. For that, a systematic electronic database search was conducted for relevant studies till 18th July 2020 in seven databases. Finally, four studies were included in the current study. The results were variable and statistical significance was not found in many of the included outcomes. These findings confirm that the overall efficacy of both approaches is nearly similar and favoring one of them over the other needs further investigations. However, the LPD procedure might have the advantage of being an MIS.

Keywords: *Laparoscopy; Open Surgery; Pancreatoduodenectomy*

Introduction

Recently, many investigations have been approached to develop advanced, safe surgical procedures with minimally invasive surgeries (MIS) to achieve the best medical service for patients undergoing such procedures. Some MIS advantages have been widely known as decreased pain, decreased blood loss, less trauma, and increased ability to pursue the daily normal activities within shorter durations. In general, MIS has been described as a baseline standard care element for some surgical procedures as appendectomy and cholecystectomy [1,2]. Moreover, it has been reported to have effectively replaced open surgeries such as upper gastrointestinal and colorectal surgeries [3-5]. For many years, the indications for using laparoscopy in pancreatic diseases were limited to staging and palliative draining of unresectable tumors. The limited use of such procedures, and especially pancreatoduodenectomy, is because of their complications that can cause serious damages and may end up with death in severely affected patients.

In 1994, laparoscopic pancreatoduodenectomy (LPD) was first described as an alternative for open pancreatoduodenectomy (OPD) [6,7]. Whipple procedure (pancreatoduodenectomy) is widely used in malignant and para-malignant lesions in the head of the pancreas and periampullary regions despite being a very complex surgical intervention [8]. Lately, the efficacy of LPD over OPD has been reported by some observational studies, conducted in high-volumed centers, in terms of reducing hospital stay and delayed gastric emptying [9,10] as a result to the growing experience in this field with many surgeons capable of conducting it safely and with achieving the proposed outcomes in both malignant and benign lesions [11]. However, disadvantages of LPD have been reported and they might include increased postoperative mortality rate, prolonged operative time, and higher readmission frequencies according to some studies [10,12,13]. Therefore, irrespective of the disadvantages and technical challenges in using LPD, it is accepted to say that it has similar efficacy to OPD in terms of overall outcomes, minimal complications, and oncological safety together with the previously mentioned advantages of being an MIS [14-17].

The number of studies conducted to investigate and compare the efficacy of LPD and OPD has been recently increasing. In 2013, a meta-analysis of six original studies was first reported in this field [18]. Later on, many systematic reviews and meta-analysis studies have been published [9,19-21]. However, the inclusion criteria for these studies mostly resulted in including studies with retrospective data only. Therefore, these studies developed a high-risk of bias due to the potential reduction in the adequate random sequence generation and blinding that is usually associated with high-quality randomized controlled trials (RCTs), and therefore, the quality of reporting evidence by these studies is poor.

Besides, a small number of RCTs in this field have been noticed which indicates the need for a systematic review that summarizes the results of these studies.

Aim of the Study

Therefore, we aim to conduct a systematic review that summarizes the results of all published RCTs that were originally developed to compare LPD and OPD.

Methods

Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review [22]. A systematic electronic database search was conducted for relevant studies till 18th July 2020 in seven databases including Google Scholar, Scopus, Web of Science (ISI), PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and CINAHL using keywords, medical subject (MeSH) terms. In databases not supporting MeSH terms, combinations of all possible terms were used. Moreover, We conducted a manual search of references from the included articles by searching the primary studies that had cited our included papers and scanning references of the relevant papers in PubMed and Google Scholar to avoid missing any relevant publications [23].

We included all relevant randomized controlled studies which are discussing Comparative assessment of Laparoscopic and Open Pancreaticoduodenectomy. Papers were excluded if there was one of the following exclusion criteria: non-human (*in vitro* or animal) studies, pilot studies, duplicate records, data could not be reliably extracted or incomplete reports, abstract only articles, thesis, books, conference papers. Title and abstract screening were done independently by four reviewers. Then, three independent reviewers performed a full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was resolved by discussion and referring to the senior author when necessary.

Data extraction

Two authors developed the data extraction sheet using the Microsoft Excel software. Data extraction was performed by three independent reviewers using the excel sheet. The fourth independent reviewer performed data checking to ensure the extracted data accuracy. All the disagreements and discrepancies were resolved by discussion and consultation with the senior author when necessary.

Quality assessment

Three independent reviewers evaluated the risk of bias in the included studies. The revised tool for assessing the risk of bias in randomized trials (RoB 2) was used to determine the quality of the included studies [24]. Quality assessment of each study was obtained through a scoring system including 5 questions. Any discrepancy between the reviewers was solved through discussion.

Results and Discussion

Search results

Initially, a total of 1496 records were retrieved; of which 512 duplicated were removed to have 984 papers for the title and abstract screening stage. Following the first screening wave, we had 45 papers for full-text screening. After excluding 41 records for different reasons, 4 studies were finally included this systematic review. Noteworthy, manual search efforts did not find any additional relevant papers.

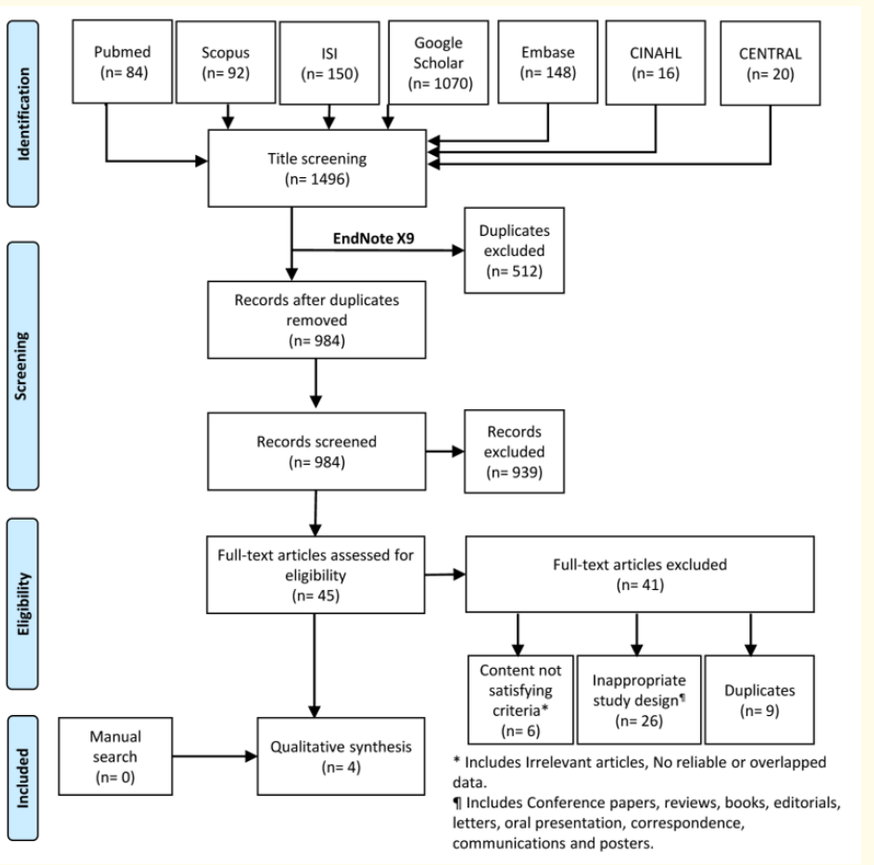

Figure 1: *PRISMA flowchart summarizing the search process in this study.*

Characteristics and bias risk of the included studies

Four studies were included in the current study with a sample size ranging from 38 to 99 individuals. The ages of included patients ranged from about 60 years old and up to 79 years old. The mean male percentage among all studies was 52%, ranging from 45.45% to 62.5% among different studies. Table 1 summarizes the main characteristics of the included studies.

Author, year	Country	Sample size	Age mean ± SD(range)	Male %	Aim	Main conclusion
Van-Hilst, 2019 [25]	Netherlands	38	(61–79)	47.36	To investigate if postoperative inflammatory markers differed between laparoscopic (LPD) and open pancreatoduodenectomy (OPD) and if there was a relationship between inflammatory markers and the occurrence of postoperative complications	LPD, as compared to OPD, did not reduce the postoperative inflammatory response. IL-6 levels were associated with postoperative complications and pancreatic fistula.
Van Hilst, 2019 [26]	Netherlands	99	(59–76)	45.45	To assess whether laparoscopic pancreatoduodenectomy could reduce time to functional recovery compared with open pancreatoduodenectomy.	Laparoscopic pancreatoduodenectomy was associated with more complication-related deaths than was open pancreatoduodenectomy, and there was no difference between groups in time to functional recovery.
Poves, 2018 [27]	Spain	61	NA	54.1	To compare perioperative outcomes of pancreatoduodenectomy (PD) performed through the laparoscopic route or by open surgery.	Laparoscopic PD versus open surgery is associated with a shorter LOS and a more favorable postoperative course while maintaining oncological standards of a curative-intent surgical resection.
Palanivelu, 2017 [14]	India	64	58.2±2.07	62.5	To compare laparoscopic and open pancreatoduodenectomy for short-term outcomes in a randomized trial.	Laparoscopy offered a shorter hospital stay than open pancreatoduodenectomy in this randomized trial.

Table 1: *Characteristics of the included studies.*

SD: Standard Deviation.

The overall risk of bias was low with some concerns in the aspects of deviation from the intended intervention, bias in the outcome measurement, and a selective reporting of the reported results (Figure 2A). None of the included studies had a high risk of bias, although one of the studies showed some concerns. The most concerning domains were a deviation from the intended intervention and outcome measurement (Figure 2B).

Comparative assessment

In this systematic review, we have summarized the results of four recently published RCTs that were under our inclusion criteria and compared the use of LPD and OPD in the management of periampullary lesions. The main outcomes of these studies include the length of hospital stay, 90-day mortality, and Clavien-Dindo 3 Complications while other secondary outcomes include bile leak, blood loss, pancreatic outcomes, reoperation, and readmission, duration of the operation and oncologic outcomes. These are discussed as follows:

Primary outcomes

Length of hospital stay

This outcome was reported by all of the included studies in this study. Specifically, only two [26,27] of them reported both the initial and total estimated hospital stay with no estimated statistical significance, while the other two [14,25] were not specific. Only Palanivelu., *et al.* [14] and Poves., *et al.* [27] reported statistical significance between the two groups with shorter durations in the LPD group. On the other hand, van Hilst., *et al.* [25,26] in his two studies (the LEOPARD-2 trial and its side study) showed no significance between the two groups although longer durations were associated with the LPD group. This is consistent with the results of previously published meta-

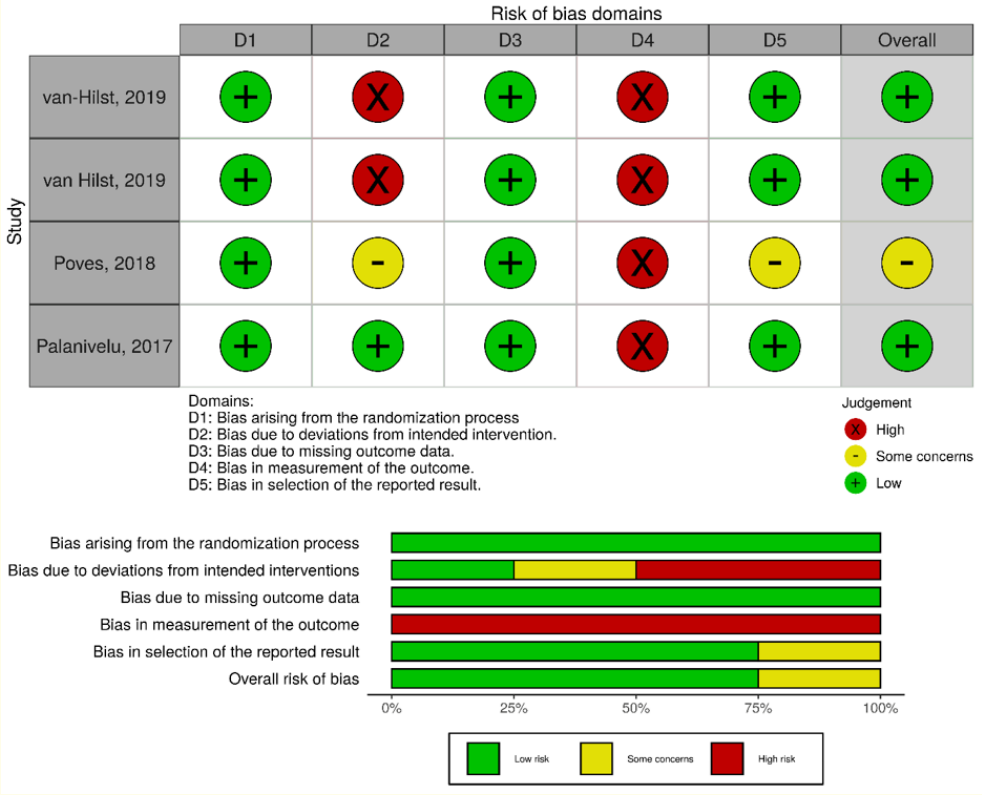

Figure 2: *Quality of the included studies. A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study (D1: bias arising from the randomization process; D2: bias due to deviations from intended interventions, D3: bias due to missing outcome data, D4: bias in measurement of the outcome, and D5: bias in selection of the reported result).*

analysis studies that reported shorter durations with LPD but with no statistical significance with an estimated moderate to high heterogeneity [28,29]. Nickel., *et al*. [29] justified this heterogeneity by the difference in healthcare services offered by the different countries where the included studies were conducted.

90-day mortality

Post-operative mortality was reported by three included studies, of whom Palanivelu., *et al*. [14] and Poves., *et al*. [27] in the PLOT and PADULAP trials, respectively, reported the all-cause mortality with no specifications while van Hilst., *et al*. [26] in the LEOPARD-2 trial was the only one to report both cancer-related and complication-related mortalities. None of these studies showed statistical significance between LPD and OPD groups. However, Palanivelu., *et al*. [14] reported total two deaths in both groups, Poves., e*t al*. [27] reported two to none deaths in the OPD and LPD groups, respectively, while van Hilst., *et al*. [26] reported three to none deaths in the LPD and OPD groups, respectively. The pooled results of the similar published meta-analysis showed similar outcomes [28,29].

Clavien-Dindo ≥ 3 complications

Similar to the 90-day mortality outcome, Clavien-Dindo ≥ 3 Complications were not statistically significant in three of the included studies [14,25,26] while Poves., *et al.* [27] study was the only one to report significance in Clavien-Dindo ≥3 outcomes between the LPD and OPD groups. Furthermore, van Hilst., *et al*. [25,26] in his two studies showed increased numbers of patients with complications in the LPD group while Palanivelu., *et al*. [14] reported the opposite. This is consistent with the overall analysis results of Nickel., *et al*. [29] and Lin., *et al* [28]. Additionally, patients with Clavien-Dindo ≥3 Complications showed higher levels of inflammatory mediators which play a significant role in developing these complications [25].

Secondary outcomes

Pancreatic and biliary-related outcomes

These outcomes include postoperative pancreatic fistula (POPF), post-pancreatectomy hemorrhage, and delayed gastric emptying. All of these outcomes were reported by all of our included trials. All of the included studies showed no statistical significance in the aforementioned variables. However, heterogeneity of the results between them was found. Specifically, POPF and delayed gastric emptying were higher in the OPD groups of two [14,27] studies while the results of van Hilst., *et al*. [25,26] favored the OPD. In terms of post-pancreatectomy hemorrhage, Poves., *et al.* [27] and van Hilst., *et al*. [25,26] results favored the LPD group while Palanivelu., *et al*. [14] results were neutral. Unlike other studies, the definition of bile leak was clearly stated in the LEOPARD-2 trial and was developed by the International Study Group of Liver Surgery [30]. In general, bile leak was reported by all of the included studies with no reported statistical significance and a mild heterogeneity in the results between the two groups.

Duration of operation and blood loss

Regarding the duration of operation, all studies reported higher and statistically significant results in the LPD group except for Palanivelu., *et al*. [14] who reported higher (but no significant) operative time in the LPD group. This is similar to the results of Nickel., *et al.* [29] and Lin., *et al.* [28] which reported overall significance. On the other hand, only three studies [14,25,26] reported the estimated post-operative blood loss, of whom only Palanivelu., *et al.* [14] reported statistical significance between the LPD and OPD groups. Nevertheless, blood loss was higher in the OPD group than LPD one in all of the three studies. Additionally, no statistical significance was reported by any of the included studies in terms of hospital readmission and reoperation.

Oncologic outcomes

R0 resection outcome was reported by three studies [14,27,26]. Despite all of these studies favored the OPD group, none of them reported statistical significance. Additionally, the numbers of harvested lymph nodes were reported by the same studies [14,27,26]. However, no statistical significance was reported by any of them and the estimated lymph node numbers were almost equal in the two groups.

Other factors and outcomes

Inflammatory response

Additionally, van Hilst., *et al.* [25] primary outcome was the inflammatory response and its association with postoperative complications. In this study, which is a side study of the LEOPARD-2 trial and in contrast to it, the authors reported interleukin-6 (IL-6) levels were not reduced when using LPD. Besides, the authors found no statistical significance between the LPD and OPD groups in patients with POPF grade B/C. IL-6 was higher in the LPD group which is suggestive of a more severe response. Although MIS approaches as LPD are meant to decrease post-operative complications via reducing the systematic inflammatory response as reported by several studies in gastrointestinal surgeries [31-35], van Hilst., *et al*. [25] results were not the same as these studies. This can be explained by the complexity and prolonged duration of pancreatoduodenectomy where LPD efficiency cannot be valid throughout the whole procedure and the

increased frequency of developing complications after pancreatoduodenectomy. Although the difference in the occurrence of complications and the presence of high levels of inflammatory mediators was not statistically significant between the LPD and OPD groups, it is still a considerable factor as the inflammatory mediators were higher in the LPD group. Another explanation is the technical efficiency and whether the performing surgeons reached the required learning curve for LPD [26,36,37].

Surgeons performance

Another factor to be accounted for is the surgical performance and the degree of experience among the conducting surgeons which have a major role in the outcomes and can be a source of bias. The importance of this feature has been previously implied after the occurrence of postoperative complications with MIS approaches [38]. Therefore, assessment of surgeons' experience and ability to conduct such procedures with high quality is essential in validating the effectiveness of LPD. Nevertheless, no standard number of procedures required to overcome the LPD learning curve have been reported. Several studies have reported variable numbers ranging between 30 and 50 cases to reach technical competency [39-41]. In this study, all of the included studies reported variable experience among their performing surgeons. Poves., *et al*. [27] reported that 15 LPD operations were conducted by the study surgeons since the start of the trial until the time of publication while Palanivelu., *et al*. [14] reported 25 at the site where the study was conducted and where a total number of 150 LPD surgeries were performed. Regarding the LEOPARD-2 trial [26], all authors underwent an LPD training program and all authors conducted this procedure on 20 patients. On the other hand, surgeons' experience with the OPD procedures is expected to be higher than with the LPD because of the wide use of this procedure by almost all centers, and all studies were conducted at high-volume centers.

Even though all of the included studies are RCTs that have better quality than retrospective investigations, limitations to our study include the limited number of included studies and the relatively small sample sizes of these studies. Looking at the results of quality assessment of the included studies, these imply the urge to conduct more RCTs with better qualities for better results.

Conclusion

In this study, we compared between LPD and OPD in terms of many outcomes. However, the results were variable and statistical significance was not found in many of these outcomes. These findings confirm that the overall efficacy of both approaches is nearly similar and favoring one of them over the other needs further investigations. However, the LPD procedure might have the advantage of being an MIS.

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