

Enhanced recovery after surgery programs in patients undergoing hepatectomy: A meta-analysis

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Abstract

AIM: To evaluate the impact of enhanced recovery after surgery (ERAS) programs in comparison with traditional care on liver surgery outcomes.

METHODS: The PubMed, EMBASE, CNKI and Cochrane Central Register of Controlled Trials databases were searched for randomized controlled trials (RCTs) comparing the ERAS program with traditional care in patients undergoing liver surgery. Studies selected for the meta-analysis met all of the following inclusion criteria: (1) evaluation of ERAS in comparison to traditional care in adult patients undergoing elective open or laparoscopic liver surgery; (2) outcome measures including complications, recovery of bowel function, and hospital length of stay; and (3) RCTs. The following exclusion criteria were applied: (1) the study was not an RCT; (2) the study did not compare ERAS with traditional care; (3) the study reported on emergency, non-elective or transplantation surgery; and (4) the study consisted of unpublished studies with only the abstract presented at a national or international meeting. The primary outcomes were complications. Secondary outcomes were length of hospital stay and time to first flatus.

RESULTS: Five RCTs containing 723 patients were included in the meta-analysis. In 10/723 cases, patients presented with benign diseases, while the remaining 713 cases had liver cancer. Of the five studies, three were published in English and two were published in Chinese. Three hundred and fifty-four patients were in the ERAS group, while 369 patients were in the traditional care group. Compared with traditional care, ERAS programs were associated with significantly decreased overall complications (RR = 0.66; 95%CI: 0.49-0.88; $P = 0.005$), grade I complications (RR = 0.51; 95%CI: 0.33-0.79; $P = 0.003$), and hospital

length of stay [WMD = -2.77 d, 95%CI: -3.87(-1.66); $P < 0.00001$]. Similarly, ERAS programs were associated with decreased time to first flatus [WMD = -19.69 h, 95%CI: -34.63(-4.74); $P < 0.0001$]. There was no statistically significant difference in grade II-V complications between the two groups.

CONCLUSION: ERAS is a safe and effective program in liver surgery. Future studies should define the active elements to optimize postoperative outcomes for liver surgery.

Key words: Enhanced recovery after surgery; Liver surgery; Complications; Hospital length of stay; Meta-analysis

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Core tip: To the best of our knowledge, this is the first meta-analysis of randomized controlled trials that have investigated the impact of enhanced recovery after surgery (ERAS) programs on surgical outcomes in liver surgery patients. The implementation of ERAS programs is safe and effective for liver surgery. However, we found some problems, which involved inconsistent outcome measures and ERAS criteria that were not specific to liver surgery. Future research in this field should develop liver surgery-specific ERAS programs.

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INTRODUCTION

The enhanced recovery after surgery (ERAS) program, or fast-track surgery (FTS), was first initiated by Kehlet *et al*^[1] in colorectal surgery during the 1990s. In the first ERAS study, the authors demonstrated accelerated recovery, shorter hospital length of stay (LoS) and reduced postoperative morbidity in the ERAS group^[2]. Since that study was published, ERAS has been strongly promoted worldwide and has revolutionized the traditional thinking and principles of behavior in the perioperative process developed over the past 100 years. Consequently, the clinical pattern of many diseases has changed. ERAS is characterized by a series of optimization measures grounded in evidence-based medicine during the perioperative period to attenuate the physical and psychological stress responses and complications, and to potentiate postoperative rehabilitation for patients following

a variety of surgical procedures^[3]. Preoperative education, epidural or regional anesthesia, perioperative fluid management, minimally invasive techniques, optimal pain control, early initiation of oral feeding, and mobilization are some of the hallmarks of ERAS programs^[4,5]. In recent years, ERAS protocols have been applied to different types of surgery, including colorectal^[6], gastric^[7], vascular^[8], urologic^[9] and gynecologic^[10] procedures.

ERAS programs have also been used during hepatic surgery^[11,12]. With the improvement of operative techniques and perioperative management, mortality after liver resection surgery has decreased to its current level of 5%. Morbidity rates, however, remain high and range from 15% to 50%^[13]. Although a number of studies have evaluated ERAS programs in relation to liver surgery, limited data have precluded proper analysis of their effectiveness. Recently, randomized controlled trials (RCTs) comparing ERAS programs with traditional care in liver surgery patients have been published. We performed a meta-analysis of the published literature to assess the safety and efficacy of ERAS programs in comparison with traditional care in patients undergoing liver surgery for liver cancer. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[14].

MATERIALS AND METHODS

Publication search

Two reviewers (Han-Teng Yang and Hao Zhang) independently performed a literature search in the PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and Cochrane Central Register of Controlled Trials databases for all RCTs that assessed the impact of ERAS programs on patients following hepatectomy in comparison to traditional care, which had been published in 1966 through November 8, 2014. We did not apply language restrictions. The following search terms were used: fast track, fast-track, enhanced recovery, liver, hepatic, hepatocellular, hepatectomy, resection, surgery, surgical, randomized controlled trial, randomized, randomly and clinical trial. Synonyms of each of the terms were also used in the search. Abstracts from each of the studies were reviewed. In addition, the references from each of the retrieved articles were manually screened to identify other potential eligible RCTs.

Inclusion and exclusion criteria

Studies selected for the meta-analysis met all of the following inclusion criteria: (1) the study evaluated ERAS in comparison to traditional care in adult patients undergoing elective open or laparoscopic liver surgery; (2) the outcome measures included complications, recovery of bowel function, and hospital LoS; and (3) the study must be an RCT. The following exclusion

criteria were applied: (1) the study was not an RCT; (2) the study did not compare ERAS with traditional care; (3) the study reported on emergency, non-elective or transplantation surgery; and (4) the study consisted of unpublished data with only the abstract presented at a national or international meeting. For different publications with overlapping data, the most complete publication was selected. Two authors (Tian-Gen Ni and Bo L) independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements, and reached a unified decision.

Data extraction

Two researchers (Han-Teng Yang and Hao Zhang) independently reviewed and extracted the following information from each of the studies: first author's name, publication year, country, total number of cases and controls, age, sex, type of surgery, outcome measures, and number of ERAS program items according to the guidelines established by the ERAS group^[15]. The core elements of ERAS include preadmission information and counseling, preoperative bowel preparation, preoperative fasting and carbohydrate loading, preanesthetic medication, prophylaxis against thromboembolism, antimicrobial prophylaxis, standard anesthetic protocol, preventing and treating postoperative nausea and vomiting, laparoscopy-assisted surgery, surgical incisions, nasogastric intubation, preventing intraoperative hypothermia, perioperative fluid management, drainage of the peritoneal cavity, urinary drainage, preventing postoperative ileus, postoperative analgesia, postoperative nutritional care and early mobilization. If there were any disagreements between the two reviewers, a third reviewer (Hai-Peng Meng) was recruited and the issue was discussed until a consensus was achieved. When multiple publications reported on the same or overlapping data, we selected the study with the most complete dataset.

Assessment of risk of bias

The methodology for each RCT was assessed independently by two reviewers (Tian-Gen Ni and Han-Teng Yang) according to the Cochrane Collaboration's risk of bias tool^[16,17], which analyzes the following criteria: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. For each entry based on the risk of bias assessment guidelines, we made a judgment (low risk of bias, high risk of bias, or uncertain). All disagreements were resolved by discussion until a consensus was achieved.

Outcome measures

Complications (defined according to the Dindo-Clavien classification^[18]) were the primary outcome measure. Secondary outcome measures included: (1) hospital

LoS (defined as the number of days in the hospital after surgery until discharge); and (2) time to first flatus.

Statistical analysis

Meta-analyses were performed by using risk ratios (RRs) for dichotomous outcomes, and weighted mean differences (WMDs) were used for continuous outcomes. Pooled estimates were presented with 95% CIs. If the included studies provided medians and interquartile ranges, we calculated the mean \pm SD according to the methods outlined by Hozo *et al.*^[19]. When heterogeneity was found to be statistically significant ($P < 0.05$ or $I^2 > 50\%$ ^[20,21]), a random effects model was applied. Otherwise, a fixed effects model was adopted to calculate the pooled RRs or WMDs. Funnel plots were generated to determine the presence of publication bias. When a study presented with significant heterogeneity, sensitivity analyses were performed to assess how inferring standard deviations from medians and interquartile ranges from poor quality studies affected the overall results. We further identified sources of heterogeneity and assessed the robustness and consistency of statistical techniques used. For all other comparisons, statistical significance was defined by $P < 0.05$ and all tests were two-tailed. All statistical analyses were performed using the Review Manager (RevMan) software, version 5.3 from the Cochrane Collaboration (<http://tech.cochrane.org/revman>). Some outcomes were not analyzed but instead were presented as descriptive information.

RESULTS

Study characteristics and assessment of bias risk

After the initial literature search, a total of 101 potentially relevant studies were identified. The final meta-analysis, after application of inclusion and exclusion criteria, included five RCTs with a total of 723 patients^[22-26]. In 10/723 cases, patients presented with benign diseases, while the remaining 713 cases had liver cancer. Of the five studies, three were published in English and two were published in Chinese. The PRISMA flow diagram is shown in Figure 1. Three hundred and fifty-four patients were in the ERAS group, while 369 patients were in the traditional care group. The sample size for the included studies ranged from 60 to 297 patients. The included RCTs were published between 2012 and 2014 and were conducted solely in adult patients. There were no multicenter trials. Characteristics of each included RCT are presented in Table 1. Each reviewer performed an assessment of risk of bias of each methodological component. The risk of bias summary for the included RCTs is presented in Figure 2.

Primary outcome measures

Overall complications were reported in all included studies. Because we did not identify significant

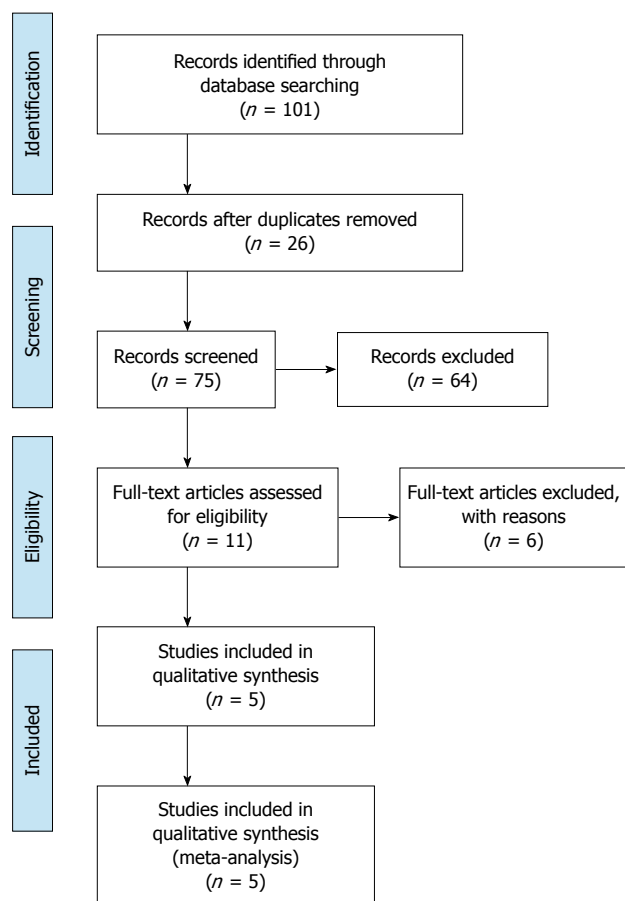


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

heterogeneity among the trials ($I^2 = 0\%$, $P = 0.93$), a fixed-effects model was applied to this meta-analysis. In the ERAS group, there was a significant reduction in overall complications (RR = 0.66, 95%CI: 0.49-0.88; $P = 0.005$) (Figure 3). Using the Dindo-Clavien classification^[18], information regarding grade I complications and grade II-V complications was available from the five studies. In the fixed-effects model, the ERAS group had significantly fewer grade I complications (RR = 0.51, 95%CI: 0.33-0.79; $P = 0.003$), without heterogeneity among the trials ($I^2 = 0\%$, $P = 0.44$) (Figure 3). However, no differences in grade II-V complications were found between the ERAS and traditional care groups (RR = 0.94, 95%CI: 0.58-1.52; $P = 0.80$), without heterogeneity among the trials ($I^2 = 0\%$, $P = 0.58$) (Figure 3).

Secondary outcome measures

In all included RCTs, hospital LoS was reported and was significantly shorter for the ERAS group than the traditional care group [WMD = -2.97 d, 95%CI: -3.18-(-2.76); $P < 0.00001$]. There was, however, significant heterogeneity among the trials ($I^2 = 91\%$, $P < 0.00001$). Due to this heterogeneity, a random effects model was applied to the studies. This analysis demonstrated that the ERAS group had a shorter

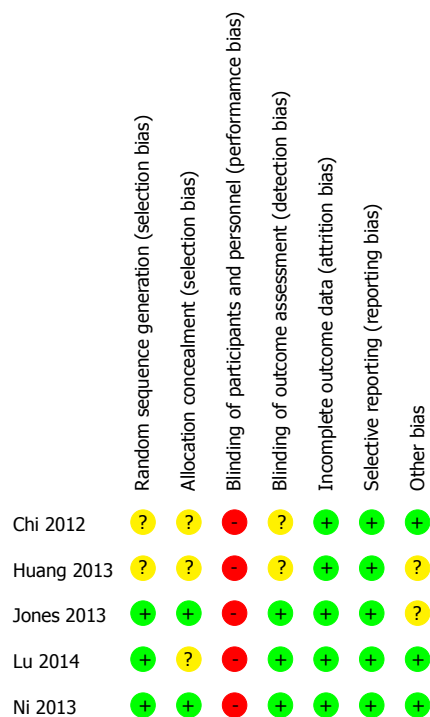


Figure 2 Risk of bias summary in included studies. The symbol of (-) red indicates that there is a high risk of bias, of (+) green indicates a low risk of bias and of (?) yellow indicates uncertainty.

hospital LoS [WMD = -2.77 d, 95%CI: -3.87-(-1.66); $P < 0.00001$] (Figure 4A). After one study was excluded^[24] due to standard deviations from medians and interquartile ranges, a sensitivity analysis did not substantially change the results of the original analysis.

Time to first flatus was reported in 4/5 studies. The heterogeneity among the trials was significant ($I^2 = 99\%$, $P < 0.00001$), thus a random effects model was applied. In the ERAS group, time to first flatus was significantly reduced in comparison to those undergoing traditional care [WMD = -19.69 h, 95%CI: -34.63-(-4.74); $P < 0.0001$] (Figure 4B).

Publication bias

Because less than 10 studies were included in this meta-analysis, we did not evaluate the publication bias for ERAS programs in patients undergoing liver surgery. In accordance with the guidelines established by the Cochrane Handbook for Systematic Reviews, the test for publication bias is unreliable when less than 10 studies are included in a meta-analysis^[27].

DISCUSSION

The aim of this meta-analysis was to evaluate the effects of ERAS programs in comparison to traditional care on patient recovery after liver surgery. Although two reviews previously concluded that ERAS programs showed lower complication rates and shorter hospital LoS in patients undergoing liver surgery^[28,29], these reviews predominantly included controlled clinical trials

Table 1 Characteristics of included trials in this meta-analysis

Trials	Year	Country	No. of patients		Age in years		Sex, M/F		Type of surgery	ERAS items
			ERAS	TC	ERAS	TC	ERAS	TC		
Jones	2013	Britain	46	45	64 (27-83)	67 (27-84)	31/15	23/22	Open, MR/mR	19
Ni	2013	China	80	80	48.4 ± 15.6	50.1 ± 21.8	66/14	59/21	Open, PH	12
Chi	2012	China	63	52	Total: 46.5 ± 5.8		80/35		Open, PH/HH	10
Huang	2013	China	30	30	NR		NR		LLR	14
Lu	2014	China	135	162	54.03 ± 11.4	52.55 ± 11.3	111/24	133/29	Open, PH	13

ERAS: Enhanced recovery after surgery; HH: Hemihepatectomy; LLR: Laparoscopic liver resection; MR: Major resection (≥ 3 segments); mR: Minor resection (< 3 segments); NR: Not reported; Open: Open surgery; PH: Partial hepatectomy; TC: Traditional care.

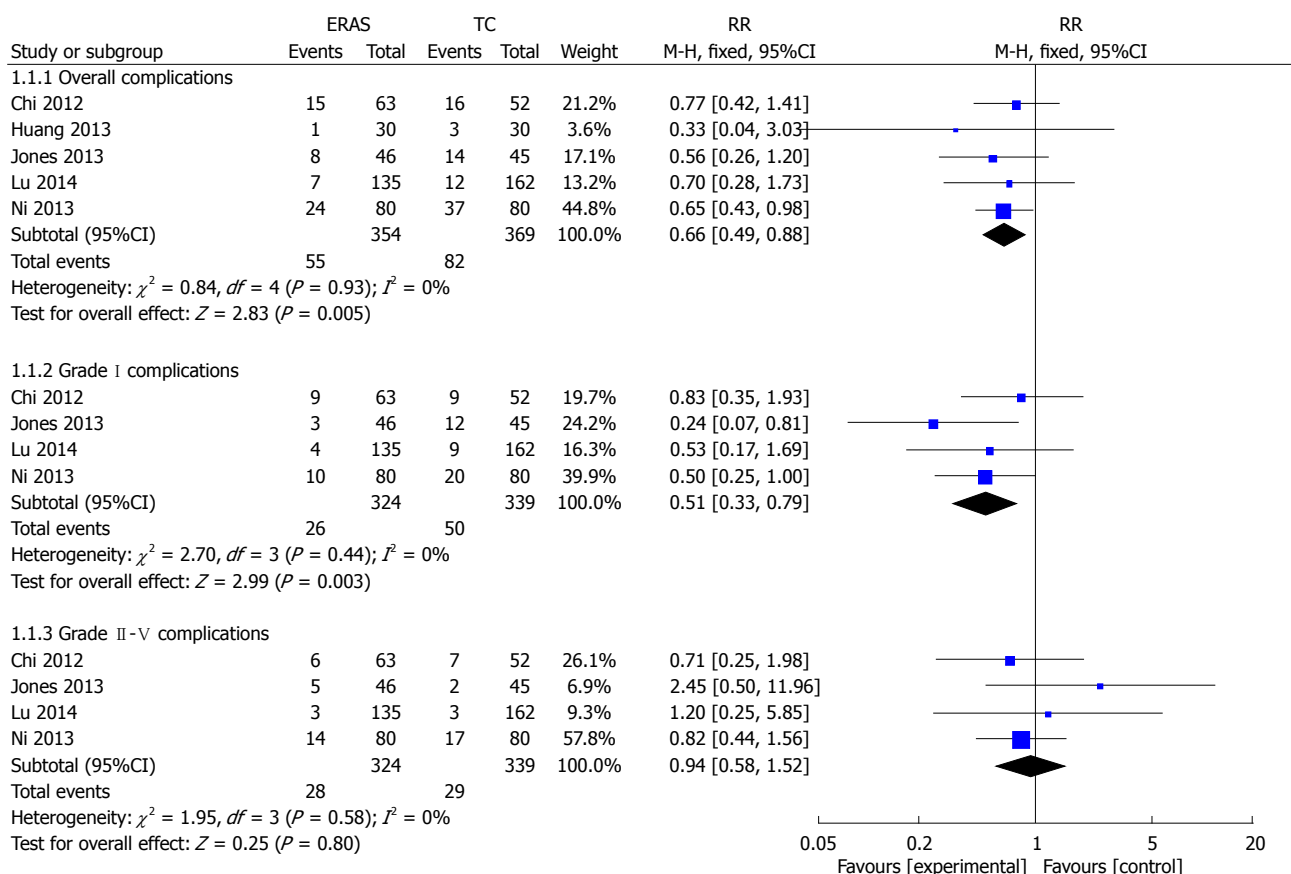


Figure 3 Forest plot of enhanced recovery after surgery programs vs traditional care for patient complications. ERAS: Enhanced recovery after surgery; TC: Traditional care.

or case-control studies. Therefore, the results of the previous analyses may not be strong enough due to a lack of sufficient data and/or the limited quality of the clinical trials. Because additional RCTs comparing ERAS to traditional care have been published since the previous two studies, the present study was warranted. This meta-analysis was performed according to the PRISMA statement^[14] and the results suggest that implementation of ERAS programs is safe and effective in liver surgery.

Compared with traditional care, ERAS programs result in a significant reduction in overall complications, grade I complications and time to first flatus. Moreover, the hospital LoS was shortened, which likely indicates a reduction in associated hospital costs.

ERAS programs in colon surgery were first initiated in 1997 by Kehlet^[3]. Over the past 17 years, ERAS programs have received worldwide attention in patient care, particularly after successful implementation and promotion in the field of colorectal surgery, which demonstrated its feasibility and superiority in clinical applications. Several studies have reported that ERAS programs significantly reduce both postoperative hospital LoS and hospital cost, without increasing the readmission rate, recurrence rate or mortality^[30,31]. In 2005 and 2009, consensus guidelines of ERAS programs were developed and modified by a collective of colorectal surgeons^[15,32]. Despite the development of these guidelines, ERAS programs have not been implemented as a standard care in many other

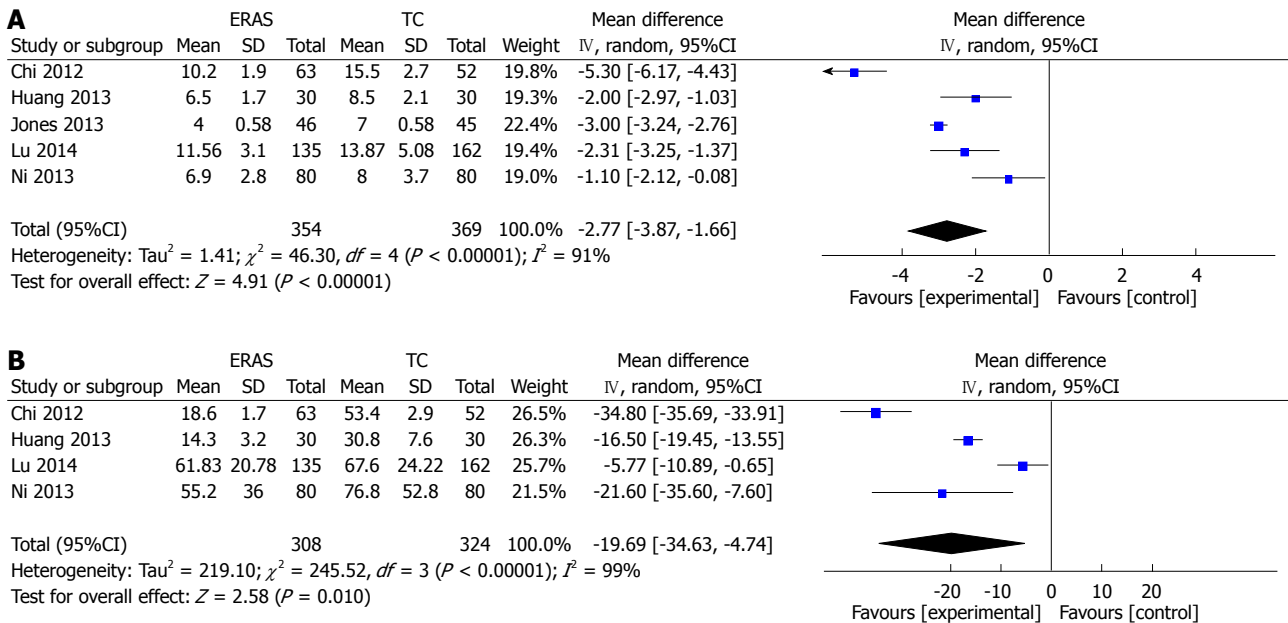


Figure 4 Forest plots of enhanced recovery after surgery programs vs traditional care for hospital length of stay (A) and time to first flatus (B). ERAS: Enhanced recovery after surgery; TC: Traditional care.

surgical fields. After MacKay *et al.*^[33] published their initial ERAS protocol for liver resection, the majority of more recent studies were either observational^[12,34] or contained limited RCTs^[11]. Few studies have compared ERAS programs with traditional care in liver surgery patients. Moreover, principles of perioperative ERAS and outcome measures have primarily been informed by literature on colorectal surgery. Because features like the patient’s physical condition, liver background, surgical complexity and postoperative residual liver function, are unique to liver surgery patients, liver surgery-specific programs should be developed to optimize ERAS protocols and outcome measures.

Although this meta-analysis included only RCTs and resulted from a rigorous search strategy with detailed inclusion and exclusion criteria, there are still limitations. For example, some studies^[22,23,25] did not provide adequate statements regarding their random sequence generation methods and allocation concealment, which could lead to selection bias. Second, the nature of the surgical research often precludes blinding of personnel and participants in the RCT, which leads to an increased risk for both performance and measurement bias. Factors such as differences in basic patient characteristics, each study’s inclusion and exclusion criteria, and the personal experience of the surgeon may also affect, to a certain extent, the stability of results. Finally, the subjective nature of the chosen endpoint and variation in data reported for outcome measures (*e.g.*, “time to flatus” and “length of stay”) suggest an underlying imprecision in the reporting of both of these outcomes, which can result in heterogeneity.

In conclusion, the results from our meta-analysis confirm that the implementation of ERAS programs

is both safe and effective in hepatectomy performed for liver cancer. ERAS reduces overall complication rates, accelerates postoperative recovery and shortens hospital LoS without increasing surgical complication rates. Future studies should determine which components of ERAS are most effective for improving outcomes in liver surgery patients.

COMMENTS

Background

Enhanced recovery after surgery (ERAS) programs have been successfully implemented in different surgical fields to improve postoperative outcomes. Despite a number of studies evaluating ERAS programs in liver surgery, their safety and effectiveness have not been systematically evaluated.

Research frontiers

In recent years, ERAS programs have been successfully implemented in colorectal, gastric and gynecologic surgical procedures. ERAS programs have also been used for hepatic surgery. This meta-analysis was performed to evaluate the safety and effectiveness of ERAS programs on liver surgery outcomes. The outcome measures in this study included complications, hospital length of stay, and the time to first flatus.

Innovations and breakthroughs

The present meta-analysis indicates that ERAS programs are safe and effective in liver surgery. ERAS reduces overall complication rates, accelerates postoperative recovery, and shortens hospital length of stay, without increasing surgical complication rates. Inconsistent and subjective outcome measures and ERAS programs that were not specific to the liver surgery field still represent limitations. Future studies should develop ERAS protocols and outcome measures optimized for the liver surgery field.

Applications

The results of this meta-analysis demonstrated the enhanced clinical effectiveness of ERAS programs in comparison to traditional care in liver surgery. ERAS programs result in a significant reduction in complications and recovery of intestinal function. Because the hospital length of stay is shortened

after ERAS implementation, the authors infer that there is also a simultaneous reduction in associated hospital costs. Thus, the implementation of ERAS programs contributes to rapid postoperative recovery in liver surgery patients.

Peer-review

In this meta-analysis of randomized controlled trials, the authors found a positive impact of ERAS programs on liver surgery outcomes when compared with traditional care. This study was well conducted and meets all of the standard requirements for a meta-analysis. The study results are clear, reliable and clinically relevant. The findings from this study are novel and applicable to a wide readership audience.

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