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Meta-Analysis

Effect of prehabilitation on outcomes following upper gastrointestinal surgery: a systematic review and meta-analysis

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ABSTRACT

It is accepted in several areas of surgery that prehabilitation can improve post-operative outcomes. Prehabilitation describes preoperative interventions aimed at optimizing patient condition prior to surgery to improve postoperative outcomes. It is hypothesized that prehabilitation reduces postoperative complications in the setting of upper gastrointestinal surgery. A systematic search strategy was performed based on a research question formulated with reference to the PICO framework. Eligible studies were those that included a predefined prehabilitation intervention, a comparison to usual care and conducted on patients undergoing upper gastrointestinal surgery. Included studies were evaluated for bias and underwent data extraction. Meta-analysis was also performed for outcomes where possible. Eight studies met criteria for inclusion in this review. The nature and length of prehabilitation programs varied widely, with interventions lasting from two to six weeks. Reported outcomes included post-operative pulmonary complications, mortality and length of hospital stay. A meta-analysis was undertaken for mortality and postoperative pulmonary complications. Meta-analysis showed postoperative pulmonary complications were reduced (RR0.68, 95% CI 0.50-0.93) in the intervention group compared to the control group, as was mortality (RR 0.59, 95% CI 0.35-1.00). Prehabilitation, especially inspiratory muscle training appears to be effective in reducing pulmonary complications in patients scheduled for upper gastrointestinal surgery. With the available data it is uncertain if this translates to reduced length of stay or mortality. There is scope for further research to better define a role for prehabilitation in upper gastrointestinal surgery, specifically the optimal prehabilitation modality and length.

Keywords: Prehabilitation, Upper GI surgery, Inspiratory muscle training, Pulmonary complications

INTRODUCTION

Prehabilitation is a preoperative intervention designed to improve a patient's condition prior to elective surgery. It is known that preoperative physical fitness determines postoperative outcome, such that increased fitness is protective in the setting of major surgery. Mechanistically it is postulated that fitter patients have increased physiological reserve to withstand surgical stress, while regular exercise might also have a beneficial ischemic preconditioning effect.[1] Prehabilitation is therefore conventionally exercise-based, but increasingly multimodal strategies are described that include inspiratory muscle training (IMT), nutritional optimization, haematinics and psychological support.[2]

These interventions collectively are intended to better prepare patients overall for surgery. Complications occurring after surgery have a number of deleterious effects, including prolonged length of hospital stay, increased healthcare cost, greater chronic disease, functional limitation and reduced quality of life.[3] It is

promising that prehabilitation has been shown to be effective in several surgical domains including orthopaedic, cardiothoracic, bariatric surgery and intra-abdominal surgery, reducing rates of all types of postoperative complications.[3-5] Upper gastrointestinal surgery carries a high rate of postoperative complications, especially pulmonary complications; it is reported upper abdominal incisions confer a 15-fold greater risk of pulmonary complications compared with lower abdominal incisions, while postoperative complication rates after some upper gastrointestinal operations may be as high as 75%. As such, upper gastrointestinal surgery is an attractive target for prehabilitation programs.[6-9]

The primary aim of this systematic review was to quantify the effect of prehabilitation on the rate of complications in upper gastrointestinal surgery. Secondary aims were to examine its effects on length of stay (LOS), quality of life and mortality, as well as to describe the nature of current prehabilitation interventions in this setting.

METHODS

Search strategy

A systematic search strategy was developed to an appropriate question formulated with reference to the PICO framework. This study was pre-registered on PROSPERO. The search strategy was undertaken in line with PRISMA guidelines, separately by two authors with a third independent author adjudicating on any disagreement regarding included papers.[10]

Four databases (MEDLINE, PUBMED, EMBASED and SCOPUS) were searched for papers published between 1st January 1999 and the 30th November 2018.

Study selection and data extraction

Criteria for inclusion of studies were inclusion of a prehabilitation intervention (defined as structured preoperative exercise or training-based intervention) inclusion a control group for comparison, conducted exclusively in the upper gastrointestinal surgery.

Exclusion criteria were studies that only involved nutritional support, only reported preoperative or physiological outcomes and involved surgeries on structures other than upper gastrointestinal tract.[1-3] Case reports, narrative reviews, systematic reviews, meta-analyses and non-English language studies were also excluded. The search identified 573 studies which were examined independently by the two authors (Figure 1). Following elimination of duplicates 476 abstracts were screened with 460 excluded. Sixteen full-text articles were reviewed with eight of these excluded with reasons (Table 1). Data extraction and potential subgroups for meta-analysis were identified in the eight remaining studies (Table 2).

Qualitative assessment

Each study was assessed using the Cochrane Risk of Bias tool.[19] This examines the risk of bias over five domains including selection, reporting, performance, detection and attrition as well as other bias derived from influences outside of these domains.

Meta-analysis

Meta-analysis was preformed using RevMan5 (20) and consisted of Mantel-Haensel test using a fixed effect model. It was reported as an odds-ratio with 95% confidence intervals.

Table 1: Excluded studies.

Study design	Author	Year	Reason excluded
Prospective cohort	Agrelli et al[11]	2012	No post-operative measurement of outcomes
RCT	Dronkers et al[12]	2008	Did not address GI surgery (AAA repair)
Retrospective cohort	Huang et al[13]	2016	No comparison to usual care as all participants received prehabilitation
Cohort	Kitahata et al[14]	2018	Peri-operative intervention rather than pre-operative
RCT (protocol)	Le roy et al[15]	2016	Protocol only
Case series	Marker et al[16]	2018	No control group
RCT	Van adrichem et al[17]	2014	No comparison to usual care
Cohort	Yamamoto et al[18]	2017	No comparison to usual care

Table 2: Characteristics of included studies.

Author	Year	Design	No. prehab	No. usual care	Intervention	Length of prehab	Outcomes assessed
Boden et al[21]	2018	RCT	218	214	Self-directed breathing exercise	Max. 6 week	PPC, mortality, LOS complications
Cho et al[25]	2014	Matched cohort	18	54	Resistance training	4 weeks	Complications, LOS

Continued.

Author	Year	Design	No. prehab	No. usual care	Intervention	Length of prehab	Outcomes assessed
Dettling et al[2(	2013	Non-randomised CT	44	39	IMT	Min 2 weeks	Lung function, PPC, complications
Dunne et al[23]	2016	RCT	19	15	High intensity interval training	4 weeks	At, sf-36, PPC, complications
Mazzola et al[27]	2017	Cohort	41	35	Nutritional support, breathing exercises, moderate exercise	5-10 days	Mortality, complications, LOS
Nakajima et al[28]	2018	Cohort	76	76	Nutritional support, physical exercise	4 weeks	6mw, mortality, LOS, PPC, complications
Soares et al[22]	2013	Non-blinded RCT	16	16	IMT, physical therapy	2-3 weeks	Complications, lung function, 6 mw, PPC, complications
Valkenet et al[24]	2018	RCT	120	121	IMT	2 weeks	PPC, complications, mortality, LOS, lung function

RCT- randomised control trial, IMT- inspiratory muscle training, PPC- pulmonary postoperative complication, LOS- length of stay, at-anaerobic threshold, 6 mw- six-minute walk test, SF-36- 36 item short form survey.

RESULTS

Study characteristics

Of the included studies, 5 were randomized control trials while the others were comparisons of an intervention group with historical controls.[12]The number of participants in these studies numbered from between 20 to 441.[21-24] These studies involved centers in Australia, New Zealand, Japan, Netherlands, Italy, Brazil, Belgium, Ireland, Finland and England.[25-28]

Surgery types

Surgical procedures were liver resections, oesophageal, gastric and pancreatic resections.[21-28]

Nature of prehabilitation programs

Studies included inspiratory muscle training (IMT) self-directed breathing exercises, physical exercise and resistance training.[22-28]Two studies additionally included nutritional programs: amino acid rich supplements and oral nutritional supports (Impact oral).[27,28]

Participants

The eight included studies captured 1122 participants with 570 receiving usual care and 552 the prescribed intervention. The average or median age reported was not below sixty in any of the included studies.

Length of intervention

The length of intervention varied between studies. All interventions lasted longer than two weeks with the longest being 6 weeks of prehabilitation prior to surgery.

Outcomes

The reported outcomes varied widely across the included studies, including clinical outcomes, physiological outcomes and quality of life metrics.

Complications

Postoperative complications were recorded in all studies most often pulmonary complications.[12.21,22] Meta-analysis showed that prehabilitation reduces both pulmonary complications (Figure 3) and complications overall (Figure 2).[24-28]

Mortality

Four studies reported on mortality as an outcome. This outcome was reported at various time periods from in hospital to 12 months post-operatively.[27,28] Following meta-analysis there was a non-significant trend towards reduced mortality as shown in figure 4.[24]

Length of stay

Length of hospital stay was reported in six studies. All but one study showed a modest non-statistically significant reduction in length of stay. By contrast, Dettling et al, showed a shorter hospital stay in the control group (median difference one and a half days). Meta-analysis for length of stay was not possible.[21.24-28]

Physiological measures

Pulmonary function was assessed using various measures including spirometry, cardiopulmonary exercise testing, maximum inspiratory pressure and inspiratory muscle endurance.[22-26]

The six minute walk test was also reported in two studies.[22-28] Measuring the volume of fat was used in one study to quantify the effect of prehabilitation on reducing visceral fat prior to surgery.[25]

All studies that measured pulmonary function reported an increase from baseline to preoperative levels following participation in a prehabilitation program. These studies also demonstrated that this improvement continued into the postoperative period.

The two studies that quantified the effect of prehabilitation on six-minute walk tests demonstrated improvement. This did not translate to statistically significant post-surgical improvement. There was no significant reduction in the volume of visceral fat in the prehabilitation group.

Quality of life

Quality of life was measured in two studies.[21,23] Dunne et al demonstrated modest improvement in SF-36 scores while Boden et al, did not report the results of the SF-36 despite including it in the study design.[29]

Evaluation of bias

The quality of the level of evidence for varied across the included studies. Most studies were small samples and assessed as low-quality evidence. Two studies, Boden et al. and Valkenet et al, were deemed to have a low risk of bias.

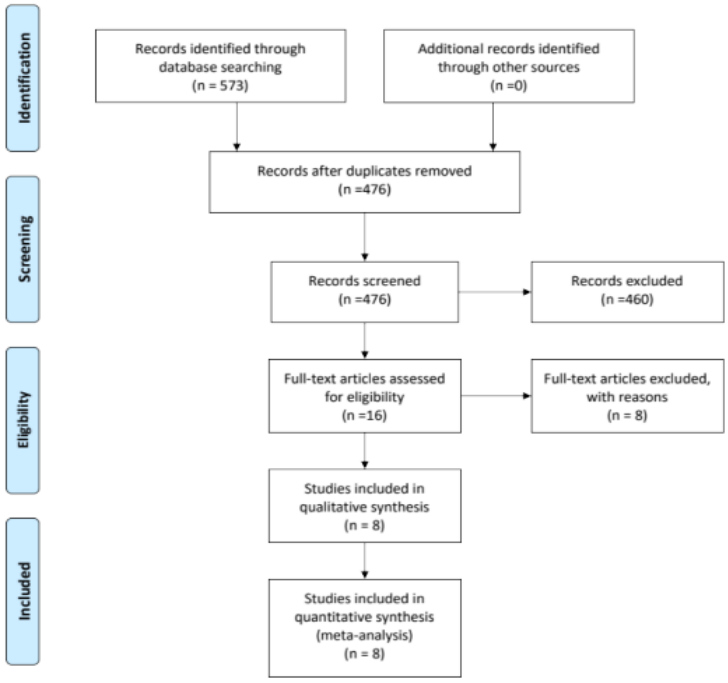


Figure 1: PRISMA flow diagram.

Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

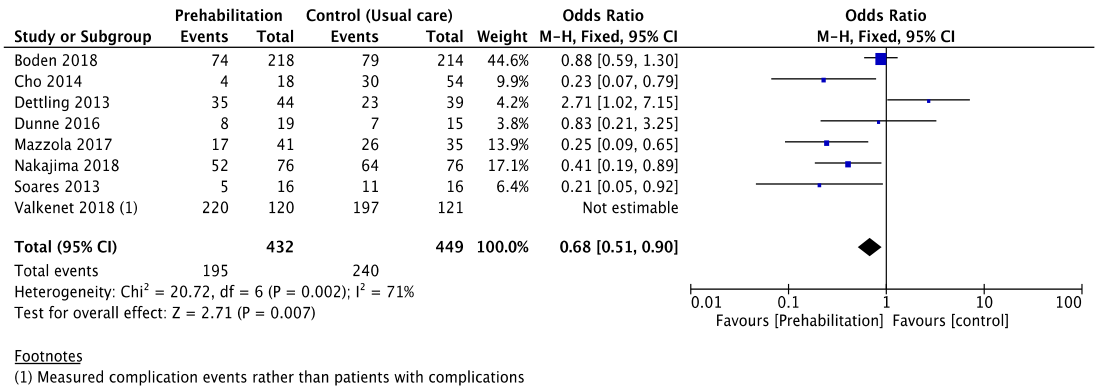


Figure 2: Effect on post-operative complications.

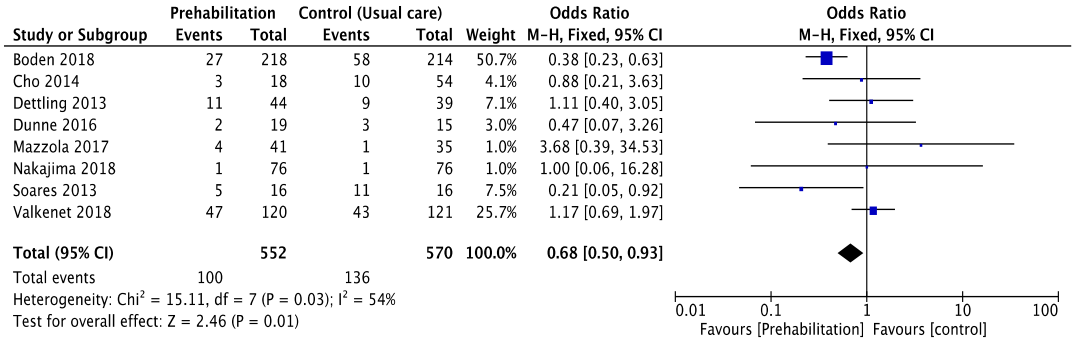
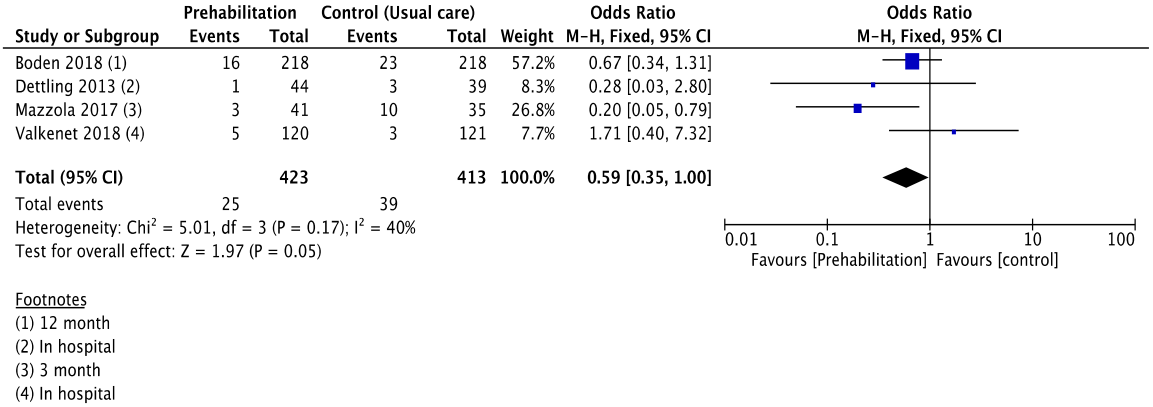


Figure 3: Effect on pulmonary complications.



Footnotes
(1) 12 month
(2) In hospital
(3) 3 month
(4) In hospital

Figure 4: Effect on mortality.

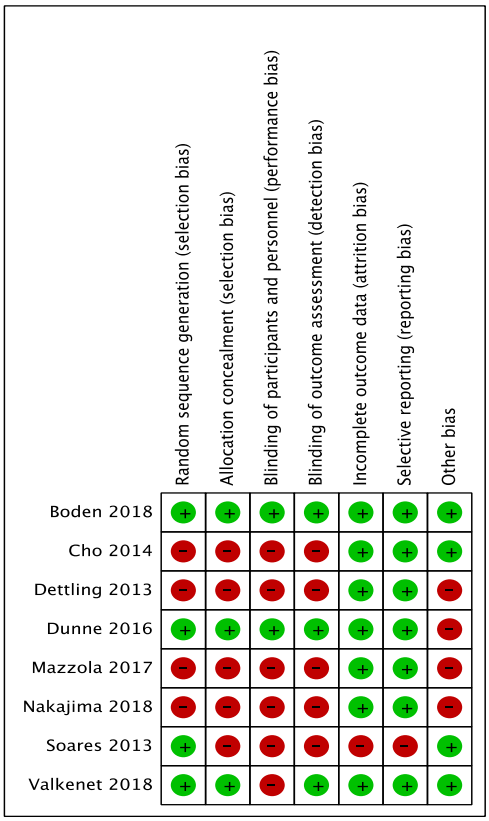


Figure 5: Evaluation of bias.

DISCUSSION

The main findings of this systematic review and meta-analysis are statistically significant reductions in both complications overall and pulmonary complications in patients receiving prehabilitation prior to upper gastrointestinal surgery compared with usual care. There was also a trend towards a reduced mortality in the prehabilitation group. Across the included studies, there was significant heterogeneity in terms of study design, modality of prehabilitation and outcome measures. Pulmonary prehabilitation was a common intervention and was found to be effective in improving clinical outcomes.[29] There was no evidence that prehabilitation caused any harm.

This is the first attempt to systematically collate evidence of preoperative interventions in the setting of upper gastrointestinal surgery. This review included a mix of surgical interventions, broadly representative of major upper gastrointestinal surgery. It also included mostly older subjects, which is typical in these surgeries. It is encouraging that prehabilitation is feasible in this patient group, especially given the increased incidences of malnutrition, frailty and reduced cardiopulmonary fitness secondary to neoadjuvant cancer treatments.[30] That said, the role of prehabilitation in younger, physiologically resilient patients is less clear based on current evidence.

The majority of the evidence in this systematic review is of low quality. Several of the included studies were retrospective cohort studies that did not account for possible confounding factors. Other studies included patients in the control groups that received non-standard care due to their perceived high risk. Only two studies were deemed to be at low risk of bias, one of which demonstrated a marked reduction in pulmonary postoperative complications (PPCs) following prehabilitation, while the other failed to show a statistically significant difference in outcomes between groups, despite improved preoperative muscle function.

The difference in findings could be explained by the lack of supervision of prehabilitation and ill-defined standard care in the latter study. In this review, supervision of prehabilitation by a trained healthcare professional was found to be an important component of effective prehabilitation and more likely to result in improved clinical outcomes. There are several limitations to this review. Despite a comprehensive review of the literature, it is possible that relevant studies were omitted due to the exclusion of non-English language studies, studies employing differing synonyms of prehabilitation and non-published literature. For the purpose of this systematic review, a broad definition of prehabilitation was employed in the search strategy, including programs that employed respiratory interventions alone.

Prehabilitation interventions have been variably described in the literature and multimodal strategies can include psychological support, haematinic optimization and smoking cessation strategies. Inclusion of these preoperative interventions may have identified more studies for data analysis, but also further increased heterogeneity in terms of interventions. Meta-analysis for all reported outcomes was not possible; a pooled effect on LOS could not be performed.

Moving forward, there is a need to further explore the effects of prehabilitation in the setting of upper gastrointestinal surgery. This group of patients are an important target for proactive interventions owing to their elevated baseline risk of postoperative complications. Prehabilitation might offer an opportunity to improve outcomes using a potentially simple preoperative intervention. Further studies should aim to delineate the optimal composition and timing of prehabilitation, in particular the role of exercise, as well as identify patient characteristics that confer greatest benefit from prehabilitation.

The optimal length of intervention to improve outcomes was not defined by this review and this would need to be explored in future studies, including whether a dose-dependent effect exists. Finally, it would be useful to identify physiological variables over the course of prehabilitation that might predict non-responders or define higher risk patients. An adequately powered randomized controlled trial is warranted to answer these unknowns. Until that time, the current available evidence suggests that the best prehabilitation intervention in upper gastrointestinal surgery is a supervised IMT program with a duration longer than 2 weeks

CONCLUSION

Prehabilitation has shown promise as a simple intervention that may reduce complications in upper gastrointestinal surgery. Reduced rates of postoperative complications need to be interpreted in the context of the low quality of evidence that currently exists. There remains much scope for future research in this area to investigate the optimal composition of prehabilitation and its effect on patient outcomes. Based on this systematic review and meta-analysis, the intervention with the strongest evidence base is IMT-based prehabilitation for at least two weeks supervised by experienced physiotherapists.

Recommendations

Prehabilitation shows promise as an intervention that may improve outcomes of Upper GI surgery. More investigation of optimal modalities and duration is required to better guide future prehabilitation programs.

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