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Gastrointestinal Recovery After Surgery: Protocol for a Systematic Review

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ABSTRACT

Introduction:

Gastrointestinal recovery after surgery is of worldwide significance. Postoperative gastrointestinal dysfunction is multifaceted and known to represent a major source of postoperative morbidity, however its significance to postoperative care across all surgical procedures is unknown. The complexity of postoperative gastrointestinal recovery is poorly defined within gastrointestinal surgery, and even less so outside this field. To inform the clinical care of surgical patients worldwide, this systematic review and meta-analysis will aim to characterise the duration of postoperative gastrointestinal recovery that can be expected across all surgical procedures and determine the associations between factors that may affect this.

Methods and analysis:

MEDLINE, Embase, Cochrane Library and CINAHL will be searched for studies reporting the time to first postoperative passage of stool after any surgical procedure. We will screen records, extract data, and assess risk of bias in duplicate. Forest plots will be constructed for time to postoperative gastrointestinal recovery, as assessed by various outcome measures. Because of potential heterogeneity, a random-effects model will be used throughout the meta-analysis. Funnel plots will be used to test for publication bias. Meta-regressions will be undertaken where the outcome is the mean time to first postoperative passage of stool, with potential predictors and confounders being patient characteristics, postoperative outcomes and surgical factors.

Ethics and dissemination:

This study will not involve human or animal subjects and thus does not require ethics approval. The outcomes will be disseminated via publication in peer-reviewed scientific journal(s) and presentations at scientific conferences.

Trial registration number: PROSPERO, CRD42021256210

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first systematic review to characterise postoperative gastrointestinal recovery across all surgical procedures.
- Findings from this study may inform the optimal postoperative care of all surgical patients, irrespective of procedure, and be applicable on a global scale.
- Future prospective research in the area of gastrointestinal recovery after surgery is likely to benefit from the proposed comprehensive characterisation of the relevant literature.
- This study will adhere to globally-accepted full systematic review methods for evidence screening, assessment of risk of bias, and data analysis to optimise reliability and translatability to global surgery.
- Given the substantial scope of the proposed research questions, it is anticipated that there will be heterogeneity within the collected data which will be acknowledged in interpreting the outcomes.

INTRODUCTION

Collections of large data help characterise broad problems in surgical care and inform the development of systems to improve patient outcomes worldwide.[1 2] Surgery is associated with diverse adverse sequelae, for which any information regarding postoperative recovery, even if unorthodox,[3] has the potential to inform beneficial multimodal interventions.[4] Optimisation of the postoperative recovery period relies, in particular, on the utilisation of both surgical and anaesthetic data.[5] Within this space, the implementation of Enhanced Recovery After Surgery (ERAS) programs across most surgical specialties has led to significant improvements to clinical outcomes and healthcare efficiency at a global level.[6]

Gastrointestinal recovery after surgery is of worldwide significance. Postoperative gastrointestinal dysfunction is multifaceted and a common form of postoperative morbidity, which frequently delays hospital discharge after surgery.[7-9] While it is accepted as prominent consideration in patients undergoing bowel surgery,[10] its significance to postoperative care across all surgical procedures is poorly defined.

As with other areas of healthcare, surgical care benefits from the application of standardised metrics.[11] For colorectal surgery, the composite measure of time to tolerance of solid food and first defaecation (GI-2) has been proposed as the best measure to assess postoperative recovery of gastrointestinal transit in that population.[12] However, a 2018 systematic review by Chapman et al concluded that postoperative ileus (reduced or uncoordinated intestinal transit resulting in prolonged postoperative gastrointestinal recovery)[10] after major colorectal surgery has no established definition, aetiology or treatment.[13] Further, for gastrointestinal surgery the outcome reporting for return of bowel function in the evidence base is variable.[14] For surgical operations outside of the field of gastrointestinal surgery, the intricacies of postoperative gastrointestinal recovery are even less defined. Therefore, to inform the clinical care of surgical patients worldwide, this systematic review and meta-analysis will aim to characterise the period of postoperative gastrointestinal recovery that can be anticipated across all surgical procedures and determine factors that may affect this.

METHODS AND ANALYSIS

The methods for this systematic review and meta-analysis, including review question, search strategy, inclusion and exclusion criteria, and risk of bias assessment, are established within this protocol prior to the conduct of the review. The study protocol was prospectively registered with PROSPERO (number CRD42021256210) and will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020)[15] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[16] reporting guidelines.

Search strategy and selection criteria

The Population, Intervention, Comparator group, Outcome (PICO) framework was used to formulate the research question and inclusion criteria. The population will be adult patients undergoing surgery. The intervention will be all surgical procedures, which will be compared against each other. The outcome will be time to first postoperative passage of stool. This will be reported in hours, and in any study reporting this metric in days, data will be converted to hours with the assumption that one day is equivalent to 24 hours. Studies will be excluded when the population is comprised of patients under the age of 18 years, if individual surgical procedure cohort sample size is less than 200, and/or if the study has an inappropriate design that precludes meaningful observational data.

The literature search will be performed by an information specialist using a peer-reviewed search strategy (Appendix 1). The search strategy will be reviewed according to Peer Review of Electronic Search Strategies (PRESS) guidelines.[17] Published literature will be identified by searching the following bibliographic databases from inception to May 2021: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Library via Wiley; and CINAHL via EBSCO. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be postoperative ileus or gastrointestinal function, after surgery, and first bowel movement. No filters will be applied to limit the retrieval by study type. Where possible, retrieval will be limited to human studies. Retrieval will not be limited by publication date or language. Searches will be supplemented by pearling of current contents, reviews, and original research relating to postoperative

gastrointestinal recovery after surgery identified through targeted searches of Google Scholar and PubMed.

Data Extraction

Two reviewers will independently screen titles and abstracts, review full texts, and extract data using a standard extraction form. Screening of titles and abstracts will be facilitated through use of a web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar).[18] Disagreements will be resolved by consensus, with a third reviewer acting as arbitrator, if required. Extracted data will include: research design, study setting, population characteristics, intervention characteristics, comparator characteristics, timeframe for follow-up, quantitative and qualitative outcomes, source(s) of funding and reported conflicts of interest, methodological quality information, and other information relevant to the review questions. Data will be synthesised in narrative and tabular formats. The primary outcome will be the time to first postoperative passage of stool. Other outcomes of interest will include, but not necessarily be limited to, time to the GI-2 composite measure (time taken for patient to tolerate solid food and to pass stool postoperatively),[12] time to first postoperative passage of flatus, time to first postoperative tolerated solid oral intake, time to first postoperative tolerated liquid oral intake, in-hospital mortality, post-admission mortality measures such as 30-day and 90-day mortality, postoperative complications, type of surgical procedure, nausea during the postoperative admission, vomiting during the postoperative admission, grade of surgery (major therapeutic vs minor therapeutic), surgical urgency (elective versus emergency), surgical approach (open vs laparoscopic vs conversion to open), postoperative length of stay, need for intensive care unit admission, medication and other factors that may influence gastrointestinal function, history of diabetes, age, sex, and other relevant surgical and perioperative datapoints. Surgical procedures will be coded according to the International Classification of Diseases, Tenth Revision (ICD-10) Procedure Codes,[19] which will inform stratification for relevant comparisons within the collected data.

Quality Assessment

Two reviewers will independently perform risk of bias assessments. Included randomised controlled trials will be appraised critically using the Cochrane Risk of Bias tool 2.0 for assessing risk of bias in randomised trials.[20] Included non-randomised observational studies will be appraised critically using the Downs and Black checklist.[21] Methodological quality of

other included study designs will be assessed using appropriate validated tools that are globally accepted.[22] The certainty of evidence will be rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and findings presented in GRADE evidence profiles and summary of findings tables[23] using standardised terms.[24 25]

Data Analysis

A meta-analysis will be undertaken using Stata Statistical Software: Release 15.1 College Station, TX: StataCorp LP. Forest plots will be constructed for mean time to first postoperative passage of stool, and subsequently for mean time to postoperative tolerance of solids, liquids, passage of flatus, and composite tolerance of solids and passage of stools.

The I^2 statistic will be used to evaluate heterogeneity (with I^2>50% indicating significant heterogeneity) as will Cochran's Q p value (with P value<0.05 indicating significant heterogeneity). In view of potential heterogeneity in this meta-analysis, a random-effects model will be used throughout. Funnel plots will be used to test for publication bias.

Meta-regression will be undertaken where the outcome is mean time to first postoperative passage of stool, with predictors and confounders being patient characteristics, postoperative outcomes and surgical factors. Univariate and multivariable meta-regressions may be performed. A P value of <0.05 will denote statistical significance.

ETHICS AND DISSEMINATION

This study will not involve human or animal subjects and thus will not require ethics approval. Results of the study will be disseminated via publication in peer-reviewed scientific journal(s) and presentations at scientific conferences.

CONCLUSIONS

This systematic review and meta-analysis will characterise many clinical aspects of the period of postoperative gastrointestinal recovery after all surgical procedures. The findings may inform the optimal postoperative care of all surgical patients, irrespective of the procedure, and be applicable on a global scale.

AUTHORS' CONTRIBUTIONS

Joshua G. Kovoor contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Brandon Stretton contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Jonathan Henry W. Jacobsen contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Aashray K. Gupta contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Christopher D. Ovenden contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Joseph N. Hewitt contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. John M. Glynatsis contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Suzanne Edwards contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Kaitryn Campbell contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Gayatri P. Asokan contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. David R. Tivey contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Wendy J. Babidge contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Christopher K. Rayner contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Adrian A. Anthony contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Markus I. Trochsler contributed to conception and design, analysis and interpretation of data, revising the article

critically for important intellectual content, and final approval of the version to be published. Michael Horowitz contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Peter J. Hewett contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Karen L. Jones contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Guy J. Maddern contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

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The authors have no competing interests.

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APPENDIX 1: Search Strategy

1. **Concept #1: Ileus/Gastrointestinal Function AND Concept #3: First Bowel Movement**
2. **Concept #2: After Surgery AND Concept #3: First Bowel Movement**
3. **Concept #1: Ileus/Gastrointestinal Function AND Concept #2: After Surgery**

Concept #1: Ileus/Gastrointestinal Function

exp Ileus/ use ppez

(Recovery of Function/ AND exp Gastrointestinal Tract/) use ppez

((ileus* OR POI OR pseudoileus OR pseudo-ileus OR ((colon* OR intestin* OR syndrome?) ADJ (pseudoobstructi* OR pseudo-obstructi*)) OR congenital short bowel syndrome? OR (enteric ADJ neuropath*) OR (obstruction syndrome? ADJ (pseudointestinal* OR pseudo-intestinal*)) OR (Ogilvie* ADJ (disease? OR syndrome?)) OR (visceral ADJ myopath*)).ti,ab,kf.) use ppez

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ2 (function* OR mobility OR motilit* OR recover*)).ti,kf.) use ppez

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ (function* OR mobility OR motilit* OR recover*)).ab.) use ppez

[Medline Ileus/Gastrointestinal Function Concept]

*Intestine pseudoobstruction/ use oemezd

*Ogilvie syndrome/ use oemezd

*Paralytic ileus/ use oemezd

*Postoperative ileus/ use oemezd

*Digestive Function/ use oemezd

exp *Gastrointestinal Motility/ use oemezd

exp *Gastrointestinal Tract Function/ use oemezd

((ileus* OR POI OR pseudoileus OR pseudo-ileus OR ((colon* OR intestin* OR syndrome?) ADJ (pseudoobstructi* OR pseudo-obstructi*)) OR congenital short bowel syndrome? OR (enteric ADJ neuropath*) OR (obstruction syndrome? ADJ (pseudointestinal* OR pseudo-

intestinal*)) OR (Ogilvie* ADJ (disease? OR syndrome?)) OR (visceral ADJ myopath*)).ti,ab,kw.) use oemezd

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ2 (function* OR mobility OR motilit* OR recover*)).ti,kw.) use oemezd

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ (function* OR mobility OR motilit* OR recover*)).ab.) use oemezd

[Embase Ileus/Gastrointestinal Function Concept]

Concept #2: After Surgery

exp Surgical Procedures, Operative/ use ppez

exp Postoperative Complications/ use ppez

exp Postoperative Period/ use ppez

(((an#esthe* ADJ2 (care OR recover*)) OR operate? OR operati* OR reoperat* OR re-operat* OR postan#esthe* OR post-an#esthe* OR postoperati* OR post-operati* OR postop? OR post-op? OR postsurg* OR post-surg* OR surgery OR surgeries OR surgical* OR surgeon?).ti,kf.) use ppez

AND

(Time/ OR Time Factors/) use ppez

((delay* OR duration? OR fast OR interval* OR length* OR long* OR period? OR prolong* OR rapid* OR short* OR slow* OR soon OR time* OR timing? OR after* OR follow* OR post*).ti,kf.) use ppez

(((after* OR follow* OR post*) ADJ3 (an#esthe* OR operate? OR operati* OR reoperat* OR re-operat* OR surgery OR surgeries OR surgical* OR surgeon?)).mp.) use ppez

[Medline After Surgery Concept]

exp *Surgery/ use oemezd

exp *Postoperative Complication/ use oemezd

exp *Postoperative Period/ use oemezd

(((an#esthe* ADJ2 (care OR recover*)) OR operate? OR operati* OR reoperat* OR re-operat* OR postan#esthe* OR post-an#esthe* OR postoperati* OR post-operati* OR

postsurg* OR post-surg* OR surgery OR surgeries OR surgical* OR surgeon?).ti,kw.) use oemezd

AND

(Time/ OR Time Factor/) use oemezd

((delay* OR duration? OR fast OR interval* OR length* OR long* OR period? OR prolong* OR rapid* OR short* OR slow* OR soon OR time* OR timing? OR after* OR follow* OR post*).ti,kw.) use oemezd

(((after* OR follow* OR post*) ADJ3 (an#esthe* OR operate? OR operati* OR reoperat* OR re-operat* OR surgery OR surgeries OR surgical* OR surgeon?)).mp.) use oemezd

[Embase After Surgery Concept]

Concept #3: First Bowel Movement

exp Constipation/ use ppez

Defecation/ use ppez

((bowel? ADJ2 (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ti,kf. use ppez

((bowel? ADJ (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ab. use ppez

AND

(Time/ OR Time Factors/) use ppez

((after* OR delay* OR duration? OR fast OR follow* OR interval* OR length* OR long* OR period? OR prolong* OR post* OR rapid* OR short* OR slow* OR soon OR time* OR timing?).mp.) use ppez

[Medline First Bowel Movement Concept]

exp *Constipation/ use oemezd

*Defecation/ use oemezd

((bowel? ADJ2 (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ti,kw. use oemezd

(((bowel? ADJ (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ab.) use oemezd

AND

(Time/ OR Time Factor/) use oemezd

((after* OR delay* OR duration? OR fast OR follow* OR interval* OR length* OR long* OR period? OR prolong* OR post* OR rapid* OR short* OR slow* OR soon OR time* OR timing?).mp.) use oemezd

[Embase First Bowel Movement Concept]

Human NOT Animal Filter

(exp animals/ OR exp animal experimentation/ OR exp animal experiment/ OR exp models animal/ OR exp vertebrate/ OR exp vertebrates/) NOT (exp humans/ OR exp human experimentation/ OR exp human experiment/)

[All results, Animal NOT Human removed]

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Gastrointestinal Recovery After Surgery: Protocol for a Systematic Review

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ABSTRACT

Introduction:

Gastrointestinal recovery after surgery is of worldwide significance. Postoperative gastrointestinal dysfunction is multifaceted and known to represent a major source of postoperative morbidity, however its significance to postoperative care across all surgical procedures is unknown. The complexity of postoperative gastrointestinal recovery is poorly defined within gastrointestinal surgery, and even less so outside this field. To inform the clinical care of surgical patients worldwide, this systematic review and meta-analysis will aim to characterise the duration of postoperative gastrointestinal recovery that can be expected across all surgical procedures and determine the associations between factors that may affect this.

Methods and analysis:

MEDLINE, Embase, Cochrane Library and CINAHL will be searched for studies reporting the time to first postoperative passage of stool after any surgical procedure. We will screen records, extract data, and assess risk of bias in duplicate. Forest plots will be constructed for time to postoperative gastrointestinal recovery, as assessed by various outcome measures. Because of potential heterogeneity, a random-effects model will be used throughout the meta-analysis. Funnel plots will be used to test for publication bias. Meta-regressions will be undertaken where the outcome is the mean time to first postoperative passage of stool, with potential predictors and confounders being patient characteristics, postoperative outcomes and surgical factors.

Ethics and dissemination:

This study will not involve human or animal subjects and thus does not require ethics approval. The outcomes will be disseminated via publication in peer-reviewed scientific journal(s) and presentations at scientific conferences.

Trial registration number: PROSPERO, CRD42021256210

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first systematic review to characterise postoperative gastrointestinal recovery across all surgical procedures.
- Findings from this study may inform the optimal postoperative care of all surgical patients, irrespective of procedure, and be applicable on a global scale.
- Future prospective research in the area of gastrointestinal recovery after surgery is likely to benefit from the proposed comprehensive characterisation of the relevant literature.
- This study will adhere to globally-accepted full systematic review methods for evidence screening, assessment of risk of bias, and data analysis to optimise reliability and translatability to global surgery.
- Given the substantial scope of the proposed research questions, it is anticipated that there will be heterogeneity within the collected data which will be acknowledged in interpreting the outcomes.

INTRODUCTION

Collections of large data help characterise broad problems in surgical care and inform the development of systems to improve patient outcomes worldwide.[1 2] Surgery is associated with diverse adverse sequelae, for which any information regarding postoperative recovery, even if unorthodox,[3] has the potential to inform beneficial multimodal interventions.[4] Optimisation of the postoperative recovery period relies, in particular, on the utilisation of both surgical and anaesthetic data that can be relied upon with certainty.[5] Within this space, the implementation of Enhanced Recovery After Surgery (ERAS) programs across most surgical specialties is an area of certainty that has led to significant improvements to clinical outcomes and healthcare efficiency at a global level.[6]

Gastrointestinal recovery after surgery is of worldwide significance. Postoperative gastrointestinal dysfunction is multifaceted and a common form of postoperative morbidity, which frequently delays hospital discharge after surgery.[7-9] While it is accepted as prominent consideration in patients undergoing bowel surgery,[10] its significance to postoperative care across all surgical procedures is an area of uncertainty that is poorly defined.

As with other areas of healthcare, surgical care benefits from the application of standardised metrics that increase certainty.[11] For colorectal surgery, the composite measure of time to tolerance of solid food and first defaecation (GI-2) has been proposed as the best measure to assess postoperative recovery of gastrointestinal transit in that population.[12] However, a 2018 systematic review by Chapman et al concluded that postoperative ileus (reduced or uncoordinated intestinal transit resulting in prolonged postoperative gastrointestinal recovery)[10] after major colorectal surgery has no established definition, aetiology or treatment.[13] Further, for gastrointestinal surgery the outcome reporting for return of bowel function in the evidence base is variable.[14] For surgical operations outside of the field of gastrointestinal surgery, the intricacies of postoperative gastrointestinal recovery are even less defined and have even more associated uncertainty. Therefore, to inform the clinical care of surgical patients worldwide, this systematic review and meta-analysis will aim to characterise the period of postoperative gastrointestinal recovery that can be anticipated across all surgical procedures and determine factors that may affect this.

METHODS AND ANALYSIS

The methods for this systematic review and meta-analysis, including review question, search strategy, inclusion and exclusion criteria, and risk of bias assessment, are established within this protocol prior to the conduct of the review. The study protocol was prospectively registered with PROSPERO (number CRD42021256210), within which the start and end dates are listed as 21 May and 31 December 2021 respectively. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020)[15] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[16] reporting guidelines will be adhered to. This protocol has followed the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 reporting guidelines (Appendix 1).[17]

Search strategy and selection criteria

The Population, Intervention, Comparator group, Outcome (PICO) framework was used to formulate the research question and inclusion criteria. The population will be adult patients undergoing surgery. The intervention will be all surgical procedures, which will be compared against each other. The outcome will be time to first postoperative passage of stool. This will be reported in hours, and in any study reporting this metric in days, data will be converted to hours with the assumption that one day is equivalent to 24 hours. Studies will be excluded when the population is comprised of patients under the age of 18 years, if individual surgical procedure or study intervention cohort sample size is less than 200, and/or if the study has an inappropriate design that precludes meaningful observational data.

The literature search will be performed by an information specialist using a peer-reviewed search strategy (Appendix 2). The search strategy will be reviewed according to Peer Review of Electronic Search Strategies (PRESS) guidelines.[18] Published literature will be identified by searching the following bibliographic databases from inception to May 2021: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Library via Wiley; and CINAHL via EBSCO. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be postoperative ileus or gastrointestinal function, after surgery, and first bowel movement. No filters will be applied to limit the retrieval by study type. Where possible, retrieval will be limited to human studies.

Retrieval will not be limited by publication date or language. Searches will be supplemented by pearling of current contents, reviews, and original research relating to postoperative gastrointestinal recovery after surgery identified through targeted searches of Google Scholar and PubMed.

Data Extraction

Two reviewers will independently screen titles and abstracts, review full texts, and extract data using a standard extraction form. Screening of titles and abstracts will be facilitated through use of a web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar).[19] Disagreements will be resolved by consensus, with a third reviewer acting as arbitrator, if required. Extracted data will include: research design, study setting, population characteristics, intervention characteristics, comparator characteristics, timeframe for follow-up, quantitative and qualitative outcomes, source(s) of funding and reported conflicts of interest, methodological quality information, and other information relevant to the review questions. Data will be synthesised in narrative and tabular formats. The primary outcome will be the time to first postoperative passage of stool. Other outcomes of interest will include, but not necessarily be limited to the following outcome factors: time to the GI-2 composite measure (time taken for patient to tolerate solid food and to pass stool postoperatively),[12] time to first postoperative passage of flatus, time to first postoperative tolerated solid oral intake, time to first postoperative tolerated liquid oral intake, in-hospital mortality, post-admission mortality measures such as 30-day and 90-day mortality, postoperative complications, nausea during the postoperative admission, vomiting during the postoperative admission, postoperative length of stay, need for intensive care unit admission, and other relevant surgical and perioperative datapoints. Further outcomes of interest will include, but not necessarily be limited to the following exposure factors: type of surgical procedure, grade of surgery (major therapeutic vs minor therapeutic), surgical urgency (elective versus emergency), surgical approach (open vs laparoscopic vs conversion to open), medication and other factors that may influence gastrointestinal function, history of diabetes, age, sex, and other relevant surgical and perioperative datapoints. The inclusion of the most commonly used surrogate measures for postoperative return of gastrointestinal function will be utilised to analyse for heterogeneity in gastrointestinal recovery after surgery. Surgical procedures will be coded according to the International Classification of Diseases, Tenth

Revision (ICD-10) Procedure Codes,[20] which will inform stratification for relevant comparisons within the collected data.

Quality Assessment

Two reviewers will independently perform risk of bias assessments. Included randomised controlled trials will be appraised critically using the Cochrane Risk of Bias tool 2.0 for assessing risk of bias in randomised trials.[21] Included non-randomised observational studies will be appraised critically using the Downs and Black checklist.[22] Methodological quality of other included study designs will be assessed using appropriate validated tools that are globally accepted.[23] The certainty of evidence will be rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and findings presented in GRADE evidence profiles and summary of findings tables[24] using standardised terms.[25 26]

Data Analysis

A meta-analysis of systematically obtained data was seen as the most appropriate study design as it provides an approach to identify, appraise, synthesise, and combine the results of the relevant studies in the global literature[16] to characterise the period of gastrointestinal recovery after any surgical procedure. This will be undertaken using Stata Statistical Software: Release 15.1 College Station, TX: StataCorp LP. Forest plots will be constructed for mean time to first postoperative passage of stool, and subsequently for mean time to postoperative tolerance of solids, liquids, passage of flatus, and composite tolerance of solids and passage of stools. Subgroup and sensitivity analyses will be performed where there are sufficient data to do so.

The I^2 statistic will be used to evaluate heterogeneity (with $I^2>50\%$ indicating significant heterogeneity) as will Cochran's Q p value (with P value<0.05 indicating significant heterogeneity). In view of potential heterogeneity in this meta-analysis, a random-effects model will be used throughout. Funnel plots will be used to test for publication bias.

Meta-regression will be undertaken where the outcome is mean time to first postoperative passage of stool, with predictors and confounders being patient characteristics, postoperative outcomes and surgical factors. The role of meta-regression in assessing the included

observational data is to summarise the existing surgical literature to characterise the period of gastrointestinal recovery after any surgical procedure. Univariate and multivariable meta-regressions may be performed. A P value of <0.05 will denote statistical significance.

Limitations

The design of this study has multiple limitations. Limiting inclusion to individual surgical procedure or study intervention cohort sample sizes of at least 200 excludes a large number of studies that would potentially contribute data to this review. However, this sample size limit was set to avoid the inclusion of smaller studies that may be accompanied by biases and outcomes that have limited reliability. Exclusion of paediatric patients under the age of 18 also limits the applicability of this study's findings to this population, however this exclusion criteria was set to prevent bias stemming from the inclusion of patients whose gastrointestinal tracts were at different stages of development. The primary outcome of time to first postoperative passage of stool has been shown in the literature to not carry the same degree of validity for measuring return of gastrointestinal function as the time to GI-2 composite measure,[12] however was selected as the primary outcome for this study as it was thought to be more widely reported across the surgical literature, particularly in study cohorts outside of general surgery and colorectal surgery. Where reported in the included studies, time to GI-2[12] will also be synthesised and analysed. To address many of the limitations of this study, we will include all adult surgical populations and any study designs reporting meaningful observational data. The broad review question of this study was set to with the aim of characterising many clinical aspects of the period of postoperative gastrointestinal recovery after all surgical procedures. Accordingly, findings from this study may inform optimal postoperative care of all surgical patients, irrespective of procedure, and be applicable on a global scale.

Patient and Public Involvement

No patients will be involved in this study.

ETHICS AND DISSEMINATION

This study will not involve human or animal subjects and thus will not require ethics approval. Results of the study will be disseminated via publication in peer-reviewed scientific journal(s) and presentations at scientific conferences. Any protocol amendments that may

arise will be appropriately disseminated within the peer-reviewed literature and academic community.

AUTHORS' CONTRIBUTIONS

Joshua G. Kovoor contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Brandon Stretton contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Jonathan Henry W. Jacobsen contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Aashray K. Gupta contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Christopher D. Ovenden contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Joseph N. Hewitt contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. John M. Glynatsis contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Suzanne Edwards contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Kaitryn Campbell contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Gayatri P. Asokan contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. David R. Tivey contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Wendy J. Babidge contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Christopher K. Rayner contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Adrian A. Anthony contributed to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. Markus I. Trochsler contributed to conception and design, analysis and interpretation of data, revising the article

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1

APPENDIX 1: PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item *(location in manuscript)*
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review ***(Title page)***
Update	1b	If the protocol is for an update of a previous systematic review, identify as such ***(Not applicable)***
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number ***(page 3)***
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author ***(Title page)***
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review ***(page 11)***
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments ***(page 9-10)***
Support:		
Sources	5a	Indicate sources of financial or other support for the review ***(Title page and page 12)***
Sponsor	5b	Provide name for the review funder and/or sponsor ***(Title page and page 12)***
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol ***(Title page and page 12)***
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known ***(page 5)***

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) ***(pages 5-6)***
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review ***(page 6)***
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage ***(pages 6-7)***
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated ***(Appendix 2)***
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review ***(pages 6-9)***
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) ***(pages 6-7)***
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators ***(pages 6-8)***
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications ***(page 7)***
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale ***(page 7)***

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis ***(page 8)***
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised ***(pages 8-9)***
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) ***(pages 8-9)***
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) ***(pages 8-9)***
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned ***(pages 8-9)***
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) ***(pages 8-9)***
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) ***(page 8)***

APPENDIX 2: Search Strategy

1. **Concept #1: Ileus/Gastrointestinal Function AND Concept #3: First Bowel Movement**
2. **Concept #2: After Surgery AND Concept #3: First Bowel Movement**
3. **Concept #1: Ileus/Gastrointestinal Function AND Concept #2: After Surgery**

Concept #1: Ileus/Gastrointestinal Function

exp Ileus/ use ppez

(Recovery of Function/ AND exp Gastrointestinal Tract/) use ppez

((ileus* OR POI OR pseudoileus OR pseudo-ileus OR ((colon* OR intestin* OR syndrome?) ADJ (pseudoobstructi* OR pseudo-obstructi*)) OR congenital short bowel syndrome? OR (enteric ADJ neuropath*) OR (obstruction syndrome? ADJ (pseudointestinal* OR pseudo-intestinal*)) OR (Ogilvie* ADJ (disease? OR syndrome?)) OR (visceral ADJ myopath*)).ti,ab,kf.) use ppez

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ2 (function* OR mobility OR motilit* OR recover*)).ti,kf.) use ppez

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ (function* OR mobility OR motilit* OR recover*)).ab.) use ppez

[Medline Ileus/Gastrointestinal Function Concept]

*Intestine pseudoobstruction/ use oemezd

*Ogilvie syndrome/ use oemezd

*Paralytic ileus/ use oemezd

*Postoperative ileus/ use oemezd

*Digestive Function/ use oemezd

exp *Gastrointestinal Motility/ use oemezd

exp *Gastrointestinal Tract Function/ use oemezd

((ileus* OR POI OR pseudoileus OR pseudo-ileus OR ((colon* OR intestin* OR syndrome?) ADJ (pseudoobstructi* OR pseudo-obstructi*)) OR congenital short bowel syndrome? OR (enteric ADJ neuropath*) OR (obstruction syndrome? ADJ (pseudointestinal* OR pseudo-

intestinal*)) OR (Ogilvie* ADJ (disease? OR syndrome?)) OR (visceral ADJ myopath*)).ti,ab,kw.) use oemezd

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ2 (function* OR mobility OR motilit* OR recover*)).ti,kw.) use oemezd

(((alimentary canal? OR alimentary tract? OR digestive* OR gastroduodenal* OR gastro-duodenal* OR gastrointestin* OR gastro-intestin* OR GI OR intestinal canal? OR intestinal tract?) ADJ (function* OR mobility OR motilit* OR recover*)).ab.) use oemezd

[Embase Ileus/Gastrointestinal Function Concept]

Concept #2: After Surgery

exp Surgical Procedures, Operative/ use ppez

exp Postoperative Complications/ use ppez

exp Postoperative Period/ use ppez

(((an#esthe* ADJ2 (care OR recover*)) OR operate? OR operati* OR reoperat* OR re-operat* OR postan#esthe* OR post-an#esthe* OR postoperati* OR post-operati* OR postop? OR post-op? OR postsurg* OR post-surg* OR surgery OR surgeries OR surgical* OR surgeon?).ti,kf.) use ppez

AND

(Time/ OR Time Factors/) use ppez

((delay* OR duration? OR fast OR interval* OR length* OR long* OR period? OR prolong* OR rapid* OR short* OR slow* OR soon OR time* OR timing? OR after* OR follow* OR post*).ti,kf.) use ppez

(((after* OR follow* OR post*) ADJ3 (an#esthe* OR operate? OR operati* OR reoperat* OR re-operat* OR surgery OR surgeries OR surgical* OR surgeon?)).mp.) use ppez

[Medline After Surgery Concept]

exp *Surgery/ use oemezd

exp *Postoperative Complication/ use oemezd

exp *Postoperative Period/ use oemezd

(((an#esthe* ADJ2 (care OR recover*)) OR operate? OR operati* OR reoperat* OR re-operat* OR postan#esthe* OR post-an#esthe* OR postoperati* OR post-operati* OR

postsurg* OR post-surg* OR surgery OR surgeries OR surgical* OR surgeon?).ti,kw.) use oemezd
AND
(Time/ OR Time Factor/) use oemezd
((delay* OR duration? OR fast OR interval* OR length* OR long* OR period? OR prolong* OR rapid* OR short* OR slow* OR soon OR time* OR timing? OR after* OR follow* OR post*).ti,kw.) use oemezd
(((after* OR follow* OR post*) ADJ3 (an#esthe* OR operate? OR operati* OR reoperat* OR re-operat* OR surgery OR surgeries OR surgical* OR surgeon?)).mp.) use oemezd
[Embase After Surgery Concept]

Concept #3: First Bowel Movement
exp Constipation/ use ppez
Defecation/ use ppez
((bowel? ADJ2 (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ti,kf. use ppez
((bowel? ADJ (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ab. use ppez
AND
(Time/ OR Time Factors/) use ppez
((after* OR delay* OR duration? OR fast OR follow* OR interval* OR length* OR long* OR period? OR prolong* OR post* OR rapid* OR short* OR slow* OR soon OR time* OR timing?).mp.) use ppez
[Medline First Bowel Movement Concept]

exp *Constipation/ use oemezd
*Defecation/ use oemezd
((bowel? ADJ2 (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ti,kw. use oemezd

(((bowel? ADJ (function* OR motilit* OR motion? OR movement?)) OR constipat* OR dyschezi? OR obstipat* OR def#ecat* OR ((excret* OR pass*) ADJ3 (f#ecal matter OR f#eces OR stool?))).ab.) use oemezd

AND

(Time/ OR Time Factor/) use oemezd

((after* OR delay* OR duration? OR fast OR follow* OR interval* OR length* OR long* OR period? OR prolong* OR post* OR rapid* OR short* OR slow* OR soon OR time* OR timing?).mp.) use oemezd

[Embase First Bowel Movement Concept]

Human NOT Animal Filter

(exp animals/ OR exp animal experimentation/ OR exp animal experiment/ OR exp models animal/ OR exp vertebrate/ OR exp vertebrates/) NOT (exp humans/ OR exp human experimentation/ OR exp human experiment/)

[All results, Animal NOT Human removed]