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Effect of perioperative intravenous lidocaine on postoperative outcomes in patients undergoing resection of colorectal cancer: a protocol for systematic review and meta-analysis

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TITLE

Effect of perioperative intravenous lidocaine on postoperative outcomes in patients undergoing resection of colorectal cancer: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Techniques using local anesthetics provide high-quality analgesia, while the anti-inflammatory properties of these drugs may represent an additional advantage. Perioperative intravenous lidocaine has shown positive effects not only on postoperative pain but also on bowel function and duration of hospital stay, due to its analgesic, anti-inflammatory and opioid-sparing effects. However, these potential benefits are not well established in patients with colorectal cancer. This research aims to determine the effect of perioperative intravenous lidocaine on postoperative outcomes in patients undergoing resection of colorectal cancer.

Methods and analysis PubMed, Embase, Web of Science, CNKI, SinoMed and WanFang Data databases were electronically retrieved to include the randomized controlled trials comparing perioperative intravenous lidocaine with placebo infusion in patients undergoing resection of colorectal cancer before September 2020. Registers of clinical trials, potential grey literature and abstracts from conferences will also be searched. Two reviewers will screen literature, extract data and assess risk of bias of studies included independently. The primary outcome variable will be restoration of intestinal function. The secondary outcome variables will consist of the severity of postoperative pain at 4, 12, 24, and 48 hours after surgery, the incidence of postoperative nausea and vomiting, and the length of hospital stay. A meta-analysis will be performed using RevMan 5.4 software provided by the Cochrane Collaboration and Stata V.12.0. Subgroup and sensitivity analyses will be conducted.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and shared on social media platforms.

PROSPERO registration number CRD42020216232.

Key words Lidocaine; Colorectal cancer; Prognosis; Meta-analysis; Systematic review; Randomized controlled trial

Word Count: 2034

Table: 1 Figure: 1

ARTICLE SUMMARY

Strengths and limitations of this study

- This research will provide the best assessment with currently available data on whether perioperative intravenous lidocaine can improve postoperative outcomes in patients undergoing resection of colorectal cancer.
- The analysis of various sources of heterogeneity and the assessment of risk of bias of the included studies will be a critical point for extracting and synthesising evidence-based conclusions.
- One limitation of this study is that differences in duration of perioperative intravenous lidocaine as interventions cannot be restricted，which will affect study results possibly.
- Notably, this research will include only patients with colorectal cancer, which differs from other meta-analyses and may be an advantage or a chanllenge.

INTRODUCTION

Perioperative intravenous lidocaine (IVL) infusion showed potential advantages in a range of surgical specialties, including hepatobiliary,[1] gynecological and colorectal surgery.[2] [3]Studies have suggested that IVL conveys postoperative benefits including reduction of postoperative pain, and shortened time to return of gastrointestinal function.[4-6]

However, a recent randomized, double-blinded, placebo-controlled trial by Herzog et al. indicated that intravenous lidocaine had no significant benefits for patients undergoing robot-assisted colorectal surgery,[7] including cumulated morphine consumption at 24h or 72h after end of surgery, considering multiple outcomes including time until first flatus or defecation, use of antiemetics and time until discharge. Current evidence placed the question whether IVL improve postoperative outcomes in patients undergoing resection of colorectal cancer in an ambiguous area. We hypothesized that for patients with colorectal cancer, perioperative lidocaine

given intravenously would improve the restoration of intestinal function, relieve pain, reduce the incidence of postoperative nausea and vomiting(PONV) and shorten the length of hospital stay (LOS) after surgery.

METHODS

This protocol has been registered on the PROSPERO (registration number: CRD42020216232) based on the PRISMA-P guidelines. The protocol will follow the Meta-analysis of Observational Studies in Epidemiology,[8] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guideline.[9]

Inclusion criteria for study selection

Types of studies

All studies designed as randomized controlled trials(RCTs) will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy of IVL on postoperative outcomes in patients undergoing resection of colorectal cancer. Exclusion criteria comprised paediatric patients, non-colorectal or emergency procedures, non-RCT methodology, and lack of any relevant clinical outcome measures. We will also exclude reviews, qualitative studies, animal trials and laboratory studies. Studies that included more than two study arms, but had IVL and placebo groups, were included and only those groups pertinent to this meta-analysis were considered.

Types of patients

Patients scheduled for resection of colorectal cancer will be included in this study. Other restrictions included age(≥18 years old) and American Society of Anesthesiologists' (ASA) physical status(Ⅰ-Ⅲ).

Types of interventions

Perioperative intravenous lidocaine is administrated as the intervention. Normal saline (NS) as placebo or no intervention could be administrated in the control groups. No consideration was given to how long the lidocaine infusion was continued after surgery, but to be eligible for inclusion, the infusion had to commence before the

surgical incision.

Types of outcome measures

Primary outcomes

The primary outcome variable is the restoration of intestinal function, including the time until first postoperative flatus and defecation. Flatus and defecation are important indications for exclusion of intestinal obstruction and restoration of intestinal function postoperatively.[10]

Secondary outcomes

The secondary outcome variables include the severity of pain measured using VAS on postoperative days at 4, 12, 24, and 48 hours after surgery, the incidence of PONV, and the LOS.

Search methods for the identification of studies

Electronic searches

Six electric databases (PubMed, Embase, Web of Science, CNKI, SinoMed and WanFang Data) will be searched without language restriction to identify RCTs published before September 2020. A search strategy has been developed for the 6 databases as a combination of “Colonic Neoplasms”, “Rectal Neoplasms”, or “Colorectal Neoplasms” in all fields and “lidocaine” or “lignocaine” in all fields and “Infusions” or “Intravenous” in all fields and “Randomized Controlled Trial” or “RCT” in all fields. The reference lists will be searched manually for potentially relevant articles.

The search strategy for PubMed is described in table 1, which will include all search terms, and other searches will be carried out based on those results. This will be suitably adapted to search in the other databases. There are no limits on language and publication status.

Table 1 Search strategy used in PubMed database

Number	Search terms
#1	"Colonic Neoplasms"[Mesh]
#2	"Rectal Neoplasms"[Mesh]

#3	"Colorectal Neoplasms"[Mesh]
#4	(colon[Title/Abstract]) OR (rectal[Title/Abstract]) OR (colorectal[Title/Abstract]) OR (proctectomy[Title/Abstract]) OR (colonic[Title/Abstract])
#5	#1 OR #2 OR #3 OR #4
#6	"Lidocaine"[Mesh]
#7	(lidocaine[Title/Abstract]) OR (lignocaine[Title/Abstract])
#8	#6 OR #7
#9	"Infusions, Intravenous"[Mesh]
#10	(intravenous) OR (infusion)
#11	#9 OR #10
#12	"Randomized Controlled Trial" [Publication Type]
#13	(RCT) OR (randomized controlled trial)
#14	#12 OR #13
#15	#5 AND #8 AND #11 AND #14

Searching other resources

We will also search PROSPERO, the International Clinical Trials Registry Platform, ClinicalTrials. gov, dissertations, and grey literature to identify systematic reviews or clinical trials related to IVL. Manual searches will be conducted for related journals and conference processes.

Data collection and analysis

Selection of studies

Two reviewers (JWT and ZXT) will will screen the search results according to the title and abstract independently. After the full text is obtained, the 2 reviewer will screen the references for potentially relevant studies. Any discord will be resolved by discussion between the two authors and an arbiter (SGL). The selection procedure for the study will be summarized and shown in a PRISMA flow chart (Figure 1).

Data extraction

Based on the inclusion criteria, a standard form of data collection will be produced

prior to data extraction. The 2 reviewers (JWT and ZXT) will independently extract data on patient baseline demographics(age, sex, ASA physical status), operative variables and details of the lidocaine administration(dose, starting point, perioperative duration and any bolus dose administered) as well as the placebo. The studies included were stratified according to whether the patients underwent open or laparoscopic resection. If the data necessary for meta-analysis of continuous variables were not available, the corresponding author was approached to provide the raw data, and if a response was not received, the technique described by Hozo et al. was employed to estimate the mean and standard deviation from the median and interquartile range [IQR].[11] When the consensus on data extraction is not available through discussion, the third reviewer (SGL) will make a decision.

Assessment of study quality

The Cochrane Collaborations tool will be used to assess selection bias, performance bias, attrition bias and reporting bias. Two reviewers (JWT and ZXT) will independently rate the quality of the RCTs and fulfill the items of risk of bias as low, high, or unclear. Any discrepancies between the 2 reviewers will be solved by a consulting group including two experts (WXD and SGL). The quality of evidence resulting from this systematic review was evaluated through the Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the level of evidence will be classified as high, medium, low, or very low.[12]

Statistical analyses and data synthesis

Review Manager, Version 5.4 will be used for data synthesis. The pooled effects of dichotomous outcomes will be analyzed as risk ratio (RR) using the Mantel-Haenszel (M-H) technique and 95% confidence intervals (CIs). The pooled effects of continuous outcomes will be analyzed using mean difference (MD) and 95% CI. A *P* value of less than 0.05 will be considered to be statistically significant.

Assessment of heterogeneity

I^2 statistic will be used to estimate statistical heterogeneity ($I^2 \leq 50\%$ as low heterogeneity, $I^2 > 50\%$ as high heterogeneity). Clinical heterogeneity will be

assessed by the 2 reviewers (JWT and ZXT) and the consulting group (WXD and SGL). If high clinical or statistical heterogeneity is observed, a random effect model will be used. Otherwise, a fixed effect model will be chosen.

Assessment of publication bias

A funnel plot will be used to assess publication bias when ten or more RCTs are available for quantitative analysis. Egger test will be performed if included studies are less than ten.[13] For Egger's test, *p* value of greater than 0.05 was determined as no significant publishing bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will attempt to recognize potential causes for the asymmetry, including poor methodological quality and true heterogeneity of studies.

Subgroup and sensitivity analyses

On detection of heterogeneity, a subgroup analysis will be carried out to judge the source of heterogeneity. The criteria for a subgroup analysis potentially include age, type of surgery, and intervention dosage, frequency and duration. Considering the significant difference in the degree of trauma between laparoscopic surgery and open surgery, a subgroup analysis of surgical methods is necessary.[14]

Sensitivity analysis will be performed to determine the robustness of aggregate estimates and to detect whether any single study accounts for a substantial proportion of heterogeneity by eliminating the included studies from the summary review one by one. If low-quality articles are deleted, then a second meta-analysis will be carried out. Comparison and discussion of the results and effect size of the two meta-analyses will be held.[15]

Trial sequential analysis

Assessment of the risk of random errors will be done by trial sequential analysis (TSA). The results of TSA will determine whether the evidence in our meta-analysis is reliable and conclusive by providing the boundaries of sample size.[16]

Patient and public involvement

Patients and the public will not participate in the study. However, once scientific

publications disseminate our findings, they are circulated across social networks so that our conclusions will potentially affect the actions of anesthesiologists and health policymakers.

Ethics and dissemination

Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and shared on social media platforms.

DISCUSSION

There has been increasing interest and evidence in the potential for IVL infusion in patients undergoing colorectal surgery. A Cochrane review analyzed a total of 68 RCTs across various surgical specialties and demonstrated an unclear effect of IVL versus placebo on pain scores, recovery of gastrointestinal function, postoperative nausea and overall opioid requirement. [17]

Specific to the field of colorectal surgery, a recently published meta-analysis within colorectal surgery provides support for the administration of perioperative IVL in terms of earlier return of gastrointestinal function, lower postoperative pain scores and reduced hospital LOS,[18] with no difference in complication rates or apparent issues surrounding local anaesthetic toxicity. Another systematic review examined the role of IVL in the setting of elective colorectal surgery and concluded that IVL provided limited benefit in the reduction of early postoperative pain and morphine requirement when compared with placebo.[19] Thus, a comprehensive systematic review and meta-analysis including new trials were warranted.

The underlying mechanisms of IVL might be multifactorial. Lidocaine has been shown to have anti-inflammatory, analgesic and opioid-sparing properties.[20 21] Furthermore, the alleviative pain and the accelerated return of bowel function seem to be contributive to other effects.

Overall, perioperative administration of lidocaine could improve the restoration of

intestinal function, relieve pain, reduce the incidence of PONV and shorten the LOS in patients undergoing resection of colorectal cancer. However, the previous meta-analyses showed very different results. Meanwhile, systemic analyses focused on the patients with colorectal cancer seem to be absent. With the updated RCTs, the results of this meta-analysis will provide advanced evidence on the efficacy of IVL in patients undergoing resection of colorectal cancer.

Author contributions BLL and JWT designed the study. BLL and BJJ were the principal investigator and guarantor. JWT, ZXT and SGL were the main coordinators of the study. JWT, ZXT, SGL and WXD conducted the study. SGL and BLL provided statistical and epidemiological support. JWT wrote the article with the support of BLL and ZXT. All the authors revised and approved the final version of the manuscript.

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Competing interests None declared.

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Figure 1 The PRISMA flow chart of the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

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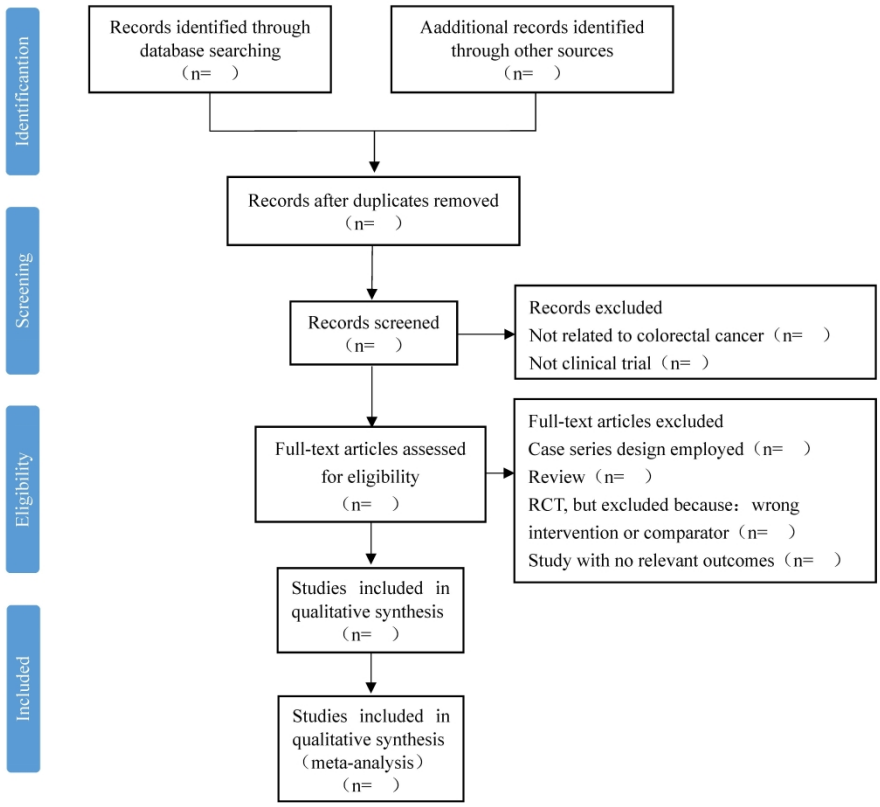

Figure 1 The PRISMA flow chart of the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

1237x1259mm (96 x 96 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
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Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	n/a
Support			
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Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4-5
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	5-6
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	5-6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - 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)	6
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	6-7

		obtaining and confirming data from investigators	
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	4-5
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4-5
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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
Data synthesis	#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 I2, Kendall's τ)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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ABSTRACT

Introduction Techniques using local anesthetics provide high-quality analgesia, while the anti-inflammatory properties of these drugs may represent an additional advantage. Perioperative intravenous lidocaine has shown positive effects not only on postoperative pain but also on bowel function and duration of hospital stay, due to its analgesic, anti-inflammatory and opioid-sparing effects. However, these potential benefits are not well established in patients undergoing resection with colorectal cancer. This research aims to determine the effect of perioperative intravenous lidocaine on postoperative outcomes in patients undergoing resection of colorectal cancer.

Methods and analysis PubMed, Embase, Web of Science, CNKI, SinoMed and WanFang Data databases were electronically retrieved to include the randomized controlled trials comparing perioperative intravenous lidocaine with placebo infusion in patients undergoing resection of colorectal cancer before August 2021. Registers of clinical trials, potential grey literature and abstracts from conferences will also be searched. Two reviewers will screen literature, extract data and assess risk of bias of studies included independently. The primary outcome variable will be long-term survival outcome, tumor recurrence and metastasis rate, and restoration of intestinal function. The secondary outcome variables will consist of the severity of postoperative pain at 4, 12, 24, and 48 hours after surgery, the incidence of postoperative nausea and vomiting, and the length of hospital stay. A meta-analysis will be performed using RevMan 5.4 software provided by the Cochrane Collaboration and Stata V.12.0. Subgroup and sensitivity analyses will be conducted.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and shared on social media platforms.

PROSPERO registration number CRD42020216232.

Key words Lidocaine; Colorectal cancer; Prognosis; Meta-analysis; Systematic review; Randomized controlled trial

Word Count: 2204

Table: 0 Figure: 1

ARTICLE SUMMARY

Strengths and limitations of this study

- This research will provide the best assessment with currently available data on whether perioperative intravenous lidocaine can improve postoperative outcomes in patients undergoing resection of colorectal cancer.
- The analysis of various sources of heterogeneity and the assessment of risk of bias of the included studies will be a critical point for extracting and synthesizing evidence-based conclusions.
- One limitation of this study is that differences in duration of perioperative intravenous lidocaine as interventions cannot be restricted, which might affect results of this study.
- Notably, this research will include only patients with colorectal cancer, which differs from other meta-analyses and may be an advantage or a challenge.

INTRODUCTION

Perioperative intravenous lidocaine (IVL) infusion showed potential advantages in a range of surgical specialties, including hepatobiliary,[1] gynecological, and colorectal surgery.[2 3] Local anesthetics may have some effects on cancer cell viability and migration.[4, 5] Several preclinical studies have shown that lidocaine has a prominent anti-tumor activity on multiple cancer cells and is a promising therapeutic agent for the treatment of cancer.[6-8] However, the effect of IVL on the postoperative outcomes of colorectal cancer patients controversial.Studies have suggested that IVL conveys postoperative benefits including reduction of postoperative pain, and shortened time to return of gastrointestinal function.[9-12]However, a recent randomized, double-blinded, placebo-controlled trial by Herzog et al. indicated that intravenous lidocaine had no significant benefits for patients undergoing robot-assisted colorectal surgery,[13] including cumulated morphine consumption at 24h or 72h after end of surgery, considering multiple outcomes including time until first flatus or defecation, use of antiemetics and time until discharge.

We hypothesized that for patients with colorectal cancer, perioperative lidocaine given intravenously would have benefits on long-term survival outcome, reduce or delay the chance of tumor recurrence or metastasis, improve the restoration of intestinal function, relieve pain, reduce the incidence of postoperative nausea and vomiting (PONV), and shorten the length of hospital stay (LOS) after surgery.

METHODS

This protocol has been registered on the PROSPERO (registration number: CRD42020216232) based on the PRISMA-P guidelines. The protocol will follow the Meta-analysis of Observational Studies in Epidemiology,[14] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guideline.[15]

Inclusion criteria for study selection

Types of studies

All studies designed as randomized controlled trials (RCTs) will be included. The current clinical trial results will be objectively integrated, which is conducive to the

evaluation of the efficacy of IVL on postoperative outcomes in patients undergoing resection of colorectal cancer. Exclusion criteria comprised paediatric patients, non-colorectal or emergency procedures, non-RCT methodology, and lack of any relevant clinical outcome measures. We will also exclude reviews, qualitative studies, animal trials and laboratory studies. Studies that included more than two study arms, but had IVL and placebo groups, were included and only those groups pertinent to this meta-analysis were considered.

Types of patients

Patients scheduled for resection of colorectal cancer will be included in this study. Other restrictions included age(≥18 years old) and American Society of Anesthesiologists' (ASA) physical status(Ⅰ-Ⅲ).

Types of interventions

Perioperative intravenous lidocaine is administrated as the intervention. Normal saline (NS) as placebo or no intervention could be administrated in the control groups. No consideration was given to how long the lidocaine infusion was continued after surgery, but to be eligible for inclusion, the infusion had to commence before the surgical incision.

Types of outcome measures

Primary outcomes

The primary outcome variable are long-term survival outcome as reported and defined by the original studies, the occurence of tumor recurrence or metastasis, and the restoration of intestinal function, including the time until first postoperative flatus and defecation. Flatus and defecation are important indications for exclusion of intestinal obstruction and restoration of intestinal function postoperatively.[16]

Secondary outcomes

The secondary outcome variables include the severity of pain measured using VAS on postoperative days at 4, 12, 24, and 48 hours after surgery, the incidence of PONV, and the LOS.

Search methods for the identification of studies

Electronic searches

Six electric databases (PubMed, Embase, Web of Science, CNKI, SinoMed and WanFang Data) will be searched without language restriction to identify RCTs published before August 2021. A search strategy has been developed for the 6 databases as a combination of "Colonic Neoplasms", "Rectal Neoplasms", or "Colorectal Neoplasms" in all fields and "lidocaine" or "lignocaine" in all fields and "Infusions" or "Intravenous" in all fields and "Randomized Controlled Trial" or "RCT" in all fields. The reference lists will be searched manually for potentially relevant articles.

The search strategy for PubMed is described in Supplementary table 1, which will include all search terms, and other searches will be carried out based on those results. This will be suitably adapted to search in the other databases. There are no limits on language and publication status.

Searching other resources

We will also search PROSPERO, the International Clinical Trials Registry Platform, ClinicalTrials. gov, dissertations, and grey literature to identify systematic reviews or clinical trials related to IVL. Manual searches will be conducted for related journals and conference processes.

Data collection and analysis

Selection of studies

Two reviewers (JWT and ZXT) will screen the search results according to the title and abstract independently. After the full text is obtained, the two reviewer will screen the references for potentially relevant studies. Any discord will be resolved by discussion between the two authors and an arbiter (SGL). The selection procedure for the study will be summarized and shown in a PRISMA flow chart (Figure 1).

Data extraction

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. The two reviewers (JWT and ZXT) will independently extract data on patient baseline demographics (age, sex, ASA physical status), operative

variables and details of the lidocaine administration (dose, starting point, perioperative duration and any bolus dose administered) as well as the placebo. The studies included were stratified according to whether the patients underwent open or laparoscopic resection. If the data necessary for meta-analysis of continuous variables were not available, the corresponding author was approached to provide the raw data, and if a response was not received, the technique described by Hozo et al. was employed to estimate the mean and standard deviation from the median and interquartile range [IQR].[17] When the consensus on data extraction is not available through discussion, the third reviewer (SGL) will make a decision.

Assessment of study quality

The Cochrane Collaborations tool will be used to assess selection bias, performance bias, attrition bias and reporting bias. Two reviewers (JWT and ZXT) will independently rate the quality of the RCTs and fulfill the items of risk of bias as low, high, or unclear. Any discrepancies between the two reviewers will be solved by a consulting group including two experts (WXD and SGL). The quality of evidence resulting from this systematic review was evaluated through the Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the level of evidence will be classified as high, medium, low, or very low.[18]

Statistical analyses and data synthesis

Review Manager, Version 5.4 will be used for data synthesis. The pooled effects of dichotomous outcomes will be analyzed as risk ratio (RR) using the Mantel-Haenszel (M-H) technique and 95% confidence intervals (CIs). The pooled effects of continuous outcomes will be analyzed using mean difference (MD) and 95% CI. A *P* value of less than 0.05 will be considered to be statistically significant.

Assessment of heterogeneity

I^2 statistic will be used to estimate statistical heterogeneity ($I^2 \leq 50\%$ as low heterogeneity, $I^2 > 50\%$ as high heterogeneity). Clinical heterogeneity will be assessed by the 2 reviewers (JWT and ZXT) and the consulting group (WXD and SGL). If high clinical or statistical heterogeneity is observed, a random effect model

will be used. Otherwise, a fixed effect model will be chosen.

Assessment of publication bias

A funnel plot will be used to assess publication bias when ten or more RCTs are available for quantitative analysis. Egger test will be performed if included studies are less than ten.[19] For Egger's test, *p* value of greater than 0.05 was determined as no significant publishing bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will attempt to recognize potential causes for the asymmetry, including poor methodological quality and true heterogeneity of studies.

Subgroup and sensitivity analyses

On detection of heterogeneity, a subgroup analysis will be carried out to judge the source of heterogeneity. The criteria for a subgroup analysis potentially include age, type of surgery, and intervention dosage, frequency and duration. Considering the significant difference in the degree of trauma between laparoscopic surgery and open surgery, a subgroup analysis of surgical methods is necessary.[20]

Sensitivity analysis will be performed to determine the robustness of aggregate estimates and to detect whether any single study accounts for a substantial proportion of heterogeneity by eliminating the included studies from the summary review one by one. If low-quality articles are deleted, then a second meta-analysis will be carried out. Comparison and discussion of the results and effect size of the two meta-analyses will be held.[21]

Trial sequential analysis

Assessment of the risk of random errors will be done by trial sequential analysis (TSA). The results of TSA will determine whether the evidence in our meta-analysis is reliable and conclusive by providing the boundaries of sample size.[22]

Patient and public involvement

Patients and the public will not participate in the study. However, once scientific publications disseminate our findings, they are circulated across social networks so that our conclusions will potentially affect the actions of anesthesiologists and health

policymakers.

Ethics and dissemination

Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and shared on social media platforms.

DISCUSSION

There has been increasing interest and evidence in the potential for IVL infusion in patients undergoing colorectal surgery. Greenwood E et al.[23] considered that there is a wide safe range of plasma concentrations by monitoring the plasma concentration of lidocaine at different time points, which provides some evidence of the safety of continuous intravenous infusion of lidocaine.

A Cochrane review analyzed a total of 68 RCTs across various surgical specialties and demonstrated an unclear effect of IVL versus placebo on pain scores, recovery of gastrointestinal function, postoperative nausea and overall opioid requirement. [24] Specific to the field of colorectal surgery, a recently published meta-analysis within colorectal surgery provides support for the administration of perioperative IVL in terms of earlier return of gastrointestinal function, lower postoperative pain scores and reduced hospital LOS,[25] with no difference in complication rates or apparent issues surrounding local anaesthetic toxicity. Another systematic review examined the role of IVL in the setting of elective colorectal surgery and concluded that IVL provided limited benefit in the reduction of early postoperative pain and morphine requirement when compared with placebo.[26] Thus, a comprehensive systematic review and meta-analysis including new trials were warranted.

The underlying mechanisms of IVL might be multifactorial. Lidocaine has been shown to have anti-inflammatory, analgesic and opioid-sparing properties,[27, 28] which can improve the restoration of intestinal function, relieve pain, reduce the incidence of PONV and shorten the LOS in patients undergoing resection of colorectal cancer.

Furthermore, lidocaine has a prominent anti-growth and anti-metastatic effects on multiple cancer cells,[7, 8] Thus, IVL may have the potential to suppress the tumor recurrence or metastasis and improve the suvival rate of colorectal cancer patients. However, previous meta-analyses showed very different results. Meanwhile, systemic reviews or meta-analyses focused on the patients with colorectal cancer and anti-tumor effect of lidocaine seem to be absent. With the updated RCTs, the results of this meta-analysis will provide the most timely and comprehensive evidence on the efficacy of IVL in patients undergoing resection of colorectal cancer.

Author contributions BLL and JWT designed the study. BLL and BJJ were the principal investigator and guarantor. JWT, ZXT and SGL were the main coordinators of the study. JWT, ZXT, SGL, WXD and LJ conducted the study. SGL and BLL provided statistical and epidemiological support. JWT wrote the article with the support of BLL and ZXT. All the authors revised and approved the final version of the manuscript.

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Competing interests None declared.

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Figure 1 The PRISMA flow chart of the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

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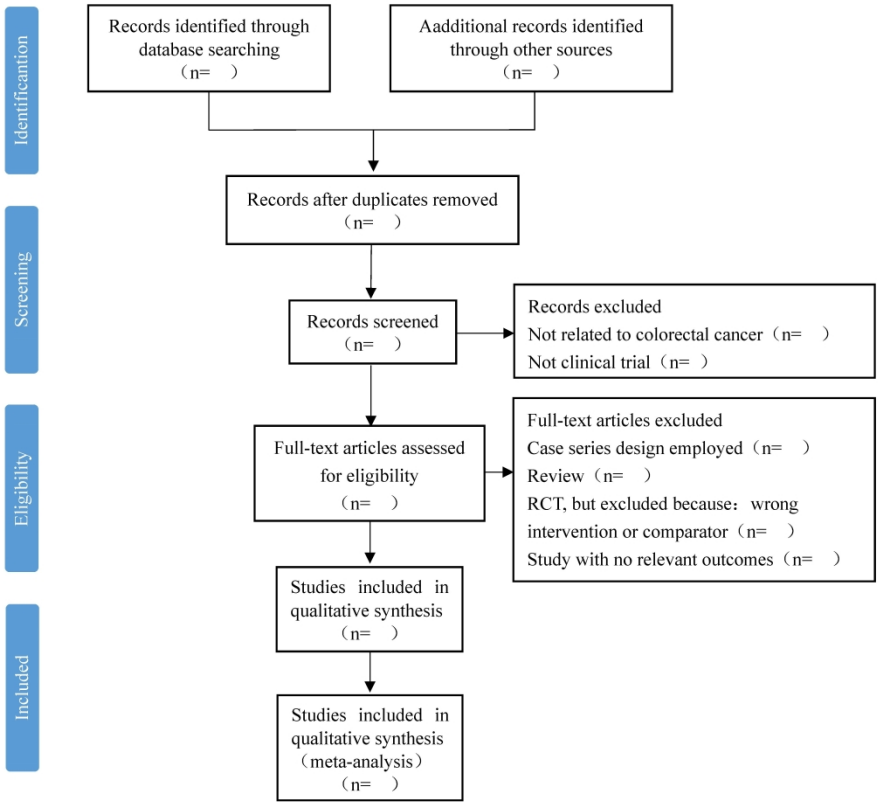

Figure 1 The PRISMA flow chart of the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

1237x1259mm (96 x 96 DPI)

Supplemental material

Supplemental Table 1 Search strategy used in PubMed database

Number	Search terms
#1	"Colonic Neoplasms"[Mesh]
#2	"Rectal Neoplasms"[Mesh]
#3	"Colorectal Neoplasms"[Mesh]
#4	(colon[Title/Abstract]) OR (rectal[Title/Abstract]) OR (colorectal[Title/Abstract]) OR (proctectomy[Title/Abstract]) OR (colonic[Title/Abstract])
#5	#1 OR #2 OR #3 OR #4
#6	"Lidocaine"[Mesh]
#7	(lidocaine[Title/Abstract]) OR (lignocaine[Title/Abstract])
#8	#6 OR #7
#9	"Infusions, Intravenous"[Mesh]
#10	(intravenous) OR (infusion)
#11	#9 OR #10
#12	"Randomized Controlled Trial" [Publication Type]
#13	(RCT) OR (randomized controlled trial)
#14	#12 OR #13
#15	#5 AND #8 AND #11 AND #14

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4-5
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	5-6
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	5-6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - 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)	6
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	6-7

		obtaining and confirming data from investigators	
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	4-5
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4-5
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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
Data synthesis	#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 I2, Kendall's τ)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7