

Effects of perioperative intravenous lidocaine infusion for postoperative pain and recovery in elderly patients undergoing surgery: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background

Improving postoperative pain and other potential benefits of IV lidocaine remains a significant debate in elderly patients. This meta-analysis aims to estimate the effect perioperative continuous IV lidocaine in elderly patients undergoing surgery.

Method

Pubmed/Medline, Web of Science, Embase and CENTRAL through OVID SP were independently searched until November 1, 2019 by two authors. This systematic review and meta-analysis included all randomized controlled trials that compared the effect of continuous IV lidocaine and any placebo or no treatment in aged patients after surgery. Primary outcomes were length of hospital stay and postoperative pain score and second outcomes were postoperative nausea and vomiting, opioid consumption, gastrointestinal recovery and postoperative neuropsychological function status scale.

Result

Eighteen studies(1175 patients) were included. Meta-analysis suggested that IV lidocaine reduce the postoperative pain scores(visual analogue scale, 0-10cm) at 2h(SMD:-1.30, 95% CI -1.90 to -0.70), 4h(SMD:-1.20, 95% CI -1.91 to -0.49), 6h(SMD:-0.87, 95%CI -1.72 to 0.02), 8h(SMD:-0.84, 95%CI -1.40 to -0.27), 12h(SMD:-0.73, 95%CI -1.14 to -0.32), 24h(SMD:-0.39, 95%CI -0.66 to -0.11), shorten length of hospital stay(MD: -0.30, 95%CI -0.50 to -0.09), decrease the requirement of opioid drugs(SMD: -0.31, 95%CI -0.31 to -0.01) and the incidence of postoperative nausea(OR: 0.52, 95%CI 0.31 to 0.87) in elderly patients undergoing surgery.

Conclusion

The evidence suggested that IV lidocaine significantly reduce postoperative pain intensity and opioid consumption and shorten the length of hospital stay in aged patients. In addition, it was shown that IV lidocaine decrease the requirement of postoperative opioid and incidence of postoperative nausea compared to control group. IV lidocaine maybe a useful assistant during general anesthesia owing to its beneficial effect in several outcomes in geriatric patients undergoing surgery.

Background

Postoperative pain management is a major focus after surgery, especially in the field of fast-track surgery, which aims to prevent or reduce common complications including postoperative pain, postoperative nausea and vomiting, hypercoagulation, deep venous thrombosis, ileus and postoperative cognitive dysfunction and speed up early recovery, in elderly patients^[1-4]. The number of major operations of all over the world annually approaches 250 million^[5] with no less than 33 percent of surgical patients over 65 year^[6, 7] and evidence reveals that postoperative pain and ileus causing extended length of hospital stay are the primary hospitalization expenses driver in the postoperative period^[8, 9]. Postoperative pain control after surgery in elderly patients has been become a serious clinical problem that many strategies have been applied to decrease postoperative pain and length of hospital stay, containing steroidal anti-inflammation drugs, non-steroidal anti-inflammatory drug (NSAID) opioid drugs, patient controlled analgesia (PCA) and local anesthesia^[10-12]. Nevertheless, none of them has indicated identical efficacy and opioid medications can caused side effects including nausea and vomiting, megrim, constipation and delay of postoperative early recovery. Recently, some studies have revealed that perioperative continuous intravenous lidocaine infusion improved postoperative outcomes in postoperative pain, consumption of opioid medications and length of hospital stay (LOS)^[13-16]. However, its effect on postoperative outcomes is not well identified due to their small sample and the deficiency of multicenter and large sample randomized controlled trials. Therefore, this review aimed to systematically assessed the effect of perioperative continuous intravenous lidocaine infusion in elderly patients undergoing surgery, in terms of postoperative pain control, postoperative opioid consumption, length of hospital stay, gastrointestinal (GI) recovery, opioid related adverse events such as postoperative nausea and vomiting (PONV) and postoperative neuropsychological function status scale.

Method

Protocol and registration

The protocol of this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) before we started to search. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[17] was followed in conducting and reporting this systematic review and meta-analysis by us (<http://www.prisma-statement.org>).

Eligibility criteria

All randomized controlled trials (RCTs) studies included were that evaluated the effect of perioperative lidocaine continuous intravenous infusion comparing with placebo, saline or blank control on at least one of relevant outcome of our interest. The intravenous lidocaine infusion must have been started preoperatively or intraoperatively (with or without an intravenous bolus) and continued until the end of surgery or a period of post-operation.

Searched database resource

Two authors independently searched electronic database Pubmed/Medline, Web of Science, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) through Ovid SP from the time of database construction to 10 November, 2019. A subject-specific search strategy was developed using in

Pubmed/Medline and applied that as the basic of the search strategies in the other electronic databases. We also scanned the reference lists and citations of included trials and any relevant systematic reviews referred to further literatures to additional trials. If necessary, we contacted trial authors to achieve additional information. We did not apply any restrictions to language and the type of surgery when searching. The literature search strategy was provided in additional file: appendix 1.

Study selection

We included the study which conformed to the following criterias:

- 1.Randomized controlled study (RCT)
- 2.Patients' age ≥ 60 years old
- 3.Undergoing surgery whether selective operation or emergency operation
- 4.Peroperative continuous intravenous lidocaine infusion
- 5.At least containing one of the outcomes of our interest and whose relative data can be exacted

Two authors respectively scanned the title and abstract of identified records to exclude uncorrelated studies and accessed the full-text articles for eligibility. We resolved any disagreements in each step by discussion or consulting the arbiter.

Data extraction

Two authors independently exacted the data of all of the included studies using standard data exaction form prepared by authors, which contained the first author, published year, study design, surgery type, population characteristics, details of lidocaine infusion and reported outcomes of our interest. If necessary, we contacted the authors of included studies by email to achieve the additional data that were missing in published. If additional information was not received, we exacted data and information from the figures. At each step of exacting data, we resolved any divergences by discussion or consulting arbiter.

Primary outcomes

- 1.Postoperative pain intensity

Pain score at rest, cough and movement (0 to10cm, 0 to 100mm visual analogue scale (VAS) and 0 to 10 numerical rating scale (NRS) at post-operation 1 hour to 48 hours)

- 2.Length of hospital stay (LOS)

Secondary outcomes

- 1.Gastrointestinal recovery (included time to defecation, time to first flatus, or time to first bowel sound)
- 2.Postoperative opioid consumption (total consumption of morphine milligramme equivalents (MEQ) in post-operation)
- 3.Postoperative nausea and vomiting (PONV)
- 4.Postoperative neuropsychological function status scale (Mini Mental State Examination (MMSE))

Risk of bias in individual studies

Two authors respectively assessed the risk of bias of all included studies. The Cochrane risk of bias tool was used to assess the risk of bias of included studies and each component was judged as low risk of bias (green), high risk of bias (red) or unclear risk of bias (yellow) and the result was shown in Fig. 2.

Summary measures and synthesis of results

For the outcome of the post-operation opioid consumption, all various opioid qualities was converted to intravenous morphine equivalent (MEQ, mg) to describe the consumption of opioid (http://www.whocc.no/atc_ddd_index).

For outcome PONV, we respectively assessed two outcomes:

- 1.Postoperative nausea containing PONV: if postoperative nausea and postoperative vomiting were not separately published.
- 2.Postoperative vomiting: if postoperative vomiting was independently reported.

When the mean and standard difference (SD) were not reported and were not obtained by contacting the relevant authors as soon as possible, they were calculated by using the median and standard error (SE) or confidence interval (CI), or the interquartile rang (IQR) if the data distribution was symmetrical^[18].

Data were analyzed using Review Manager, version 5.3.5 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom).

For continuous data, if studies measured data on the same way and scale, the mean difference (MD) was obtained from the difference between experimental group and control group with mean values and SD and if studies assessed the same outcome but measured it with different scales or ways, the standardized mean difference (SMD) was used.

For dichotomous outcomes, the odds ratio (OR) was assessed from experimental and control group event rates and 95%CI was calculated.

Random effect model was used to analyse the combined data which was assumed that clinical heterogeneity existed. The I^2 statistics was used to report the heterogeneity, which was classified by applying Cochrane Handbook of Systematic Reviews of Interventions and when $I^2 > 50\%$, it was considered the existence of obvious heterogeneity. Further, if $I^2 > 50\%$, a several subgroup analyses and sensitivity analysis were conducted to evaluate the source of heterogeneity and to assess the subpopulation of patients that could probably obtain benefits from the intervention. Subgroup analysis was performed in outcomes of length of hospital stay grouped by the type of surgery and sensitivity analysis was performed in postoperative pain score. Funnel plots were used to check the publication bias.

Result

Search result

We present the results of literature search in a PRISMA flow chart (Fig. 1). 3789 records were identified through database searching. After duplicating, screening the initial title and abstract, 81 full texts were retrieved for comprehensive evaluation. Finally, 18 RCTs were included which contained 1175 patients met the inclusion criteria in the present meta-analysis included in the final analyses.

Study characterizes

The patients of these 18 RCTs whose average age older than 60. These articles contained 595 patients in lidocaine groups and 580 patients who received normal saline or nothing served as control. Studies were carried through in patients undergoing abdominal, cardiac, orthopedic, urinary, endoscopic surgery. Nine of the studies reported surgery time, and all studies mentioned duration of infusion. A lidocaine bolus (1-2mg/kg) was given before surgical incision in 17 of the 18 RCTs whereas all eligible RCTs followed by a continuous infusion during and after operation. The characteristics of the included trials were summarized in Table 1.

Risk of bias within studies

We evaluated the quality of the included RCTs on the basis of the Cochrane Handbook of Systematic Reviews of Interventions, version 5.1.0 (updated March 2011)^[18]. The entire risk of bias concerning selection bias, performance bias, attrition bias, detection bias and other bias exposed low risk of bias in more than 65% across all included all studies (Fig. 2 and Fig. 3).

Primary outcomes

1. Postoperative pain

Postoperative pain was evaluated by different pain scores. The pain scores were provided in totally 11 studies of 18 RCTs which had sufficient quantitative data to be combined through meta-analysis^[19-29]. Five studies assessed postoperative pain on a visual analogue scale (VAS) from 0 to 100mm and five studies used the VAS from 0 to 10cm measurement, while one trial evaluated postoperative pain with NRS.

1.1 Pain score at rest

As shown in Fig. 4, postoperative pain scores at rest were evaluated in 10 studies^[19-28]. Meta-analysis of pain data at rest was statistically significant decrease VAS scores in lidocaine group compared with the control group at 2h (7 studies, n=386, SMD -1.30 95%CI -1.90 to -0.70), at 4h (7 studies, n=364, SMD -1.20 95%CI -1.91 to -0.49), at 6h (3 studies, n=208, SMD -0.87 95%CI -1.72 to -0.02), at 8h (5 studies, n=284, SMD -0.84 95%CI -1.40 to -0.27), at 12h (4 studies, n=267, SMD -0.73 95%CI -1.14 to -0.32), at 18h (3 studies, n=208, SMD -0.79 95%CI -1.78 to 0.20), at 24h (10 studies, n=569, SMD -0.39 95%CI -0.66 to -0.11), at 48h (8 studies, n=458, SMD -0.25 95%CI -0.59 to 0.10). The outcome adequately revealed that perioperative intravenous lidocaine infusion can reduced postoperative pain scores in elderly patients of abdominal, cardiac, orthopedic, urinary, endoscopic surgery at 2h, 4h, 6h, 8h, 12h, 24h after surgery, but did not decreased the pain scores at 18h and 48h after surgery.

1.2 Pain score at movement

There were 4 trials reported the pain scores postoperatively at movement^[22-24, 29]. The pain score at movement after surgery was decreased with intravenous lidocaine at 2h (2 studies, n=151, SMD -1.02 95%CI -2.05 to -0.00), 12h (2 studies, n=151, SMD -0.84 95%CI -1.18 to -0.51), one study of Moeen^[24] demonstrated yield similar effect at 6h (n=111, SMD -1.42 95%CI -1.84 to -1.01) and at 18h (n=111, SMD -0.70 95%CI -1.09 to -0.32); although there was no statistical differences at 4h (1 studies, n=40, SMD -0.58 95%CI -1.21 to 0.05), at 24h (4 studies, n=277, SMD -0.10 95%CI -0.51 to 0.30), at 48h (4 studies, n=277, SMD -0.15 95%CI -0.56 to 0.26). The detailed result are showed in Fig. 6.

We performed the robust of the evidence by sensitivity analysis, The difference of the combined effect was detected by different effect model. The estimated effect(95%CI) for the sensitivity analysis remained robust about the pain scores at different point times from 2h to 48h after surgery when selecting random effect model or fixed effect model, which showed that the results were reliable.

2.Length of hospital stay

17 trials^[19-24, 26-36] of 18 RCTs reported the length of hospital stay between groups. The overall pooled results from the meta-analysis showed that lidocaine markedly shortened the time of hospital stay compared with the control group. Intervention substantial heterogeneity was noted (MD -0.30 95%CI -0.50 to -0.09); forest plot is shown in Fig. 7.

In 3 studies^[26, 32, 34] of the 18 RCTs, lidocaine in cardiac surgery as the intervention was effective in shorting duration of hospital stay (MD -0.71 95%CI -1.37 to -0.05); Nevertheless, results from 8 studies^[19-22, 28, 29, 35, 36] in gastrointestinal surgery were not shown to reducing length of hospital stay (MD -0.20 95%CI -0.54 to 0.14) ;6 studies^[23, 24, 27, 30, 31, 33] in other surgery revealed yielded lidocaine infusion can decreased the length of hospital stay (MD -0.30 95%CI -0.50 to -0.09).

Secondary outcomes

1. Postoperative opioid consumption

Eleven articles with 552 patients reported the outcome of postoperative opioid consumption. Morphine was applied for postoperative pain relief in 6 trials^[20, 23, 25, 27, 30, 33], 4 trials^[19, 21, 26, 28] applied fentanyl, one trial^[29] offered meperidine. Pooled meta-analysis revealed the lidocaine group had fewer opioid requirements (MEQ, mg) after surgery in comparison to the control group (SMD -0.31 95%CI -0.61 to -0.01).

2. Gastrointestinal recovery

Six studies^[20, 25, 29, 30, 33, 35] with 285 patients reported data on the time to first flatus and the time to first defaecation/bowel movement.

2.1 Time to first flatus

The combined analysis did not demonstrate a significant reduction of time to flatus in lidocaine group compared with the control group (MD -3.24 95%CI -9.90 to 3.41).

2.2 Time to first defaecation/bowel movement

There was enough evidence of effect for lidocaine infusion in contrast with the control group to shorten the time to first defaecation/bowel movement (MD -8.64 95%CI -16.00 to -1.28).

3. Postoperative neuropsychological function status scale

Only one studies^[34] proved lidocaine administration during and after surgery does not reduce the high rate of postoperative cognitive dysfunction.

4. Adverse events

The complication of nausea was reported in 9 trials^[19, 21, 22, 27-29, 33, 35, 36], whereas three articles^[19, 21, 28] showed the complication of vomiting. It illustrated respectively that there was significant reduction in nausea in lidocaine group contrasted with control group (n=479 OR 0.56 95%CI 0.37 to 0.84). There was no statistical difference about vomiting between lidocaine group and control group (n=120 OR 0.47 95%CI 0.19 to 1.1) but there was a slightly lower incidence of vomiting in lidocaine group when compared with the control group.

Risk of bias across studies

The funnel plot was used to investigated the risk of bias across studies (publication bias). For outcome of postoperative pain, the funnel plot at 24h after surgery suggested funnel plot asymmetry on visual inspection, publication bias was likely to be present (Fig. 5). The funnel plot for the duration of hospital stay suggested funnel plot was symmetrical on visual inspection, indicating that publication bias was not likely to be present (Fig. 8).

Additional analysis

Additional analyses such as subgroup analysis, sensitivity analysis and publication bias analysis were performed to evaluate which surgery may benefit from IV lidocaine administration (subgroup analysis), the robust of result in terms of risk of bias from single study (sensitivity analysis) and the appearance of risk of bias across analysis (publication bias). By this means we researched the primary outcome, such as subgroup analysis for length of hospital stay, sensitivity analysis for postoperative pain at 24h after surgery and publication bias analysis for length of hospital stay and postoperative pain at 24h after surgery.

1. Subgroup analysis. The preplanned subgroups analysis on type of surgery accounted for heterogeneity about all subgroups (Fig. 7). Subgroup analysis was conducted and it was shown that IV lidocaine short the length of hospital stay only in cardiac surgery subgroup and other surgery subgroup compared to control, however, in gastrointestinal surgery subgroup, it was not statistical difference, which may be resulted by the small effect of IV lidocaine in shortening length of hospital stay for aged patients and a weaker physiological state in old folks , however, heterogeneity of three group was accepted ($I^2 < 50\%$). This result indicated that aged patients undergoing cardiac surgery may more likely benefit from perioperative IV lidocaine and the debate that whether perioperative IV lidocaine shorten the length of hospital stay in aged patients undergoing gastrointestinal surgery may resolved by more high qualities and large simple size RCTs in the future.
2. Sensitivity analysis. We tested the robust of the evidence by sensitivity analysis in the outcome of postoperative pain score due to the heterogenicity was unacceptable ($I^2 > 50\%$). The difference of the combined effect was detected by comparing fixed effect model and random effect model. The estimated

effect(95%CI) for the sensitivity analysis remained robust about the pain scores at 2h, 4h, 6h, 8h, 12h, 24h, 48h after surgery when selecting different effect model, which showed that the results were reliable. However, the estimated effect(95%CI) for the sensitivity analysis did not remained robust at 18h (RE model: SMD -0.79 95%CI -1.78 to 0.20 VS FE model: SMD -0.69 95%CI -0.98 to -0.41). The outcome adequately revealed the result of postoperative pain score at 18h was unreliable.

Discussion

Summary of evidence

This review was the first meta-analysis to evaluate the effect of perioperative continuous IV infusion of lidocaine for postoperative pain management and recovery in elderly patients undergoing surgery. It was proved that perioperative continuous IV lidocaine infusion is an effective intervention to reduce postoperative pain at 2 h, 4 h, 6 h, 8 h, 12 h, 24 h, at rest and at 6 h, 8 h, 18 h at movement for aged patients after surgery and decrease the length of hospital stay in elderly patients undergoing cardiac surgery and other type surgery. However, the most interesting of this review was that subgroup analysis revealed that continuous IV lidocaine infusion cannot reduce the length of hospital stay in aged patients undergoing gastrointestinal surgery, which was contrary to other meta-analysis^[37, 38] result of IV lidocaine comparing to control group that was IV lidocaine reduce length of hospital stay in adult undergoing gastrointestinal surgery. It might explain the opposite result that aged patient is enormously different from adult in physiology, psychology and any other fields. Furthermore, there is a lower incidence of adverse event of opioid related, postoperative nausea, in the lidocaine group. Nevertheless, there is no statistical significance in postoperative vomiting between IV lidocaine group and control group. In addition, there was less requirement of opioid consumption in IV lidocaine group compared to placebo or no treatment of control group and there was a lower risk of postoperative nausea, which is related to opioid using to some extent.

The mechanism of potential analgesia effect and other potential benefits of IV lidocaine remains unclear^[39]. Two explanations that were selective suppression of pain transfer in spinal marrow and blocking the sodium channel of mechanosensitive nociceptor have been reported to interpret the mechanism of reduction pain of IV lidocaine. In addition, IV lidocaine has also revealed anti-inflammatory benefits^[40]. Previous studies have demonstrated that IV lidocaine reduced the level of inflammatory mediators^[41]. Therefore, the mechanism that IV lidocaine reduce postoperative pain require more animal experiments and clinical trials to provide a stronger evidence.

Perfect postoperative analgesia benefits early rapid postoperative recovery and reduction of postoperative complications. However, single model analgesia is adequate for aged patients after surgery and multimodal analgesia is recommended to decrease postoperative pain intensity, opioid consumption and short length of hospital stay. Some published articles^[13, 42–44] have shown that IV lidocaine reduced pain and shorten length of hospital stay, in addition, there was a lower inflammatory in IV lidocaine and lower risk of postoperative nausea and vomiting. Thus, IV lidocaine was more preferred to use in intraoperation and after surgery.

Postoperative pain control was one of the major focuses in geriatric patients to improve postoperative recovery and life quality, reduce inquietude and get out of bed as early as possible. In this study, it was proved that IV lidocaine notably lessen the postoperative pain scores compared to placebo or no treatment at all time point at rest and at 2 h, 4 h, 6 h, 8 h and 12 h at cough or movement. Although the heterogeneity was large, we did not perform subgroup analysis owing to the studies included in every time point is small when performed subgroup analysis. The heterogeneity maybe be explained by that the duration time of IV lidocaine and the end of point were inconsistent.

In our review, the length of hospital stay of IV lidocaine compared to control group was statistical difference, however, the heterogeneity was large, which was contrast to some articles and meta-analyses^[9, 24, 45]. Thus, subgroup analysis was conducted and it was shown that IV lidocaine short the length of hospital stay only in cardiac surgery subgroup and other surgery subgroup compared to control, however, in gastrointestinal surgery subgroup, it was not statistical difference. It might explain the opposite result that aged patient is enormously different from adult in physiology, psychology and any other fields. Furthermore, it might be explained that the studies included are single center and small sample size study.

Although a massive of studies^[20, 34, 35, 46] have affirmed that the IV lidocaine was associated with a opioid-sparing effect in geriatric patients undergoing surgery, there was lack of dependable evidence. Meta-analysis can enhance statistical power and enlarger sample size by uniting results of previously published studies, which could provide a stronger evidence. Our present meta-analysis indicated that perioperative IV lidocaine could significantly reduce postoperative pain intensity, length of hospital stay in cardiac surgery, opioid consumption and postoperative nausea.

Limitations

In order to reduce the risk of bias of this present meta-analysis, we included only RCTs which all were high qualities evidence. However, there were some potential limitations in this study.

Firstly, the during time of IV lidocaine, the first bolus, the dose of continuous IV lidocaine, type of surgery and time of surgery were inconsistent, which may affect the final result such as some important data insufficient making it difficult to analysis and short time of follow up leading to underestimate in side effect.

Secondly, all the included studies are single center, small sample size studies, therefore, a larger sample size and multicentre clinical trials need to be designed and performed. And what we mentioned above may be the one resource of the heterogeneous in this review.

Thirdly, the heterogeneous outcome published was also a limitation. Although subgroup and sensitivity analysis was performed to make it lower, however, not all planned subgroup and sensitivity analysis could be carry out due to insufficient data reported. Thus, the heterogeneity could not always be explicated. At last, the range of published year of all included studies was large, which was from 1995 to 2019.

Despite the limitations above, our review is the first meta-analysis from RCTs to interpret the effect of perioperative continuous IV lidocaine for pain management in elderly patients after surgery and we clearly illustrate that IV lidocaine significantly reduce postoperative pain and opioid consumption. High quality RCTs with multicentre and a large sample size are required to assess the adequate analgesia protocol and other potential benefits of IV lidocaine in future studies.

Conclusion

The evidence that IV lidocaine, when compared with placebo or no treatment, significantly reduce postoperative pain scores, especially in the early period of post-operation and opioid consumption in geriatric patients undergoing surgery. IV lidocaine has shown limited benefit to reduce length of hospital stay in cardiac surgery and the incidence of postoperative nausea, however, there was no statistical significance in the aspect of shorting length of hospital stay in gastrointestinal surgery and other surgery in aged patients.

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials; MD: Mean difference; SMD: Standard mean difference; OR: Odds ratio ; IV: Intravenous; NSAID: Non-steroidal anti-inflammatory drug; PCA: Patient controlled analgesia; LOS: Length of hospital stay; GI: Gastrointestinal; PONV: Postoperative nausea and vomiting; RCT: Randomized controlled trial; VAS: Visual analogue scale; NRS: Numerical rating scale; MEQ: Morphine milligramme equivalents; SD: Standard difference ; SE: Standard error; CI: Confidence interval; IQR: Interquartile rang

Declarations

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YHZ and FW have contributed equally to this review. Any disagreements was resolved by consulting LY and TZ and they revised the manuscript critically. All authors read and approved the final manuscript.

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References

1. J C, R S, M B: Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta anaesthesiologica Scandinavica* 2006, 50(3):265-282.
2. PF W, H K, JM N, T S, DB C, F C: The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. *Anesthesia and analgesia* 2007, 104(6):1380-1396, table of contents.
3. L R, R L, M L: New approaches and old controversies to postoperative pain control following cardiac surgery. *European journal of anaesthesiology* 2006, 23(7):539-550.
4. PF W: Cost-effective multimodal analgesia in the perioperative period: Use of intravenous vs. oral acetaminophen. *Journal of clinical anesthesia* 2019:109625.
5. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet (London, England)* 2008, 372(9633):139-144.
6. Monk TG, Price CC: Postoperative cognitive disorders. *Current opinion in critical care* 2011, 17(4):376-381.
7. J S, RO R, TN W, A NC, DS K, RC P, AC H, DR S, DO W: Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *British journal of anaesthesia* 2017, 119(2):316-323.
8. Kehlet H: Postoperative ileus—an update on preventive techniques. *Nature clinical practice Gastroenterology & hepatology* 2008, 5(10):552-558.
9. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LH, Poepping DM, Afshari A, Kranke P: Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *British journal of anaesthesia* 2016, 116(6):770-783.
10. Basak F, Hasbahceci M, Sisik A, Acar A, Ozel Y, Canbak T, Yucel M, Ezberci F, Bas G: Glisson's capsule cauterisation is associated with increased postoperative pain after laparoscopic cholecystectomy: a prospective case-control study. *Annals of the Royal College of Surgeons of England* 2017, 99(6):485-489.
11. Abdulla S, Eckhardt R, Netter U, Abdulla W: A randomized, double-blind, controlled trial on non-opioid analgesics and opioid consumption for postoperative pain relief after laparoscopic cholecystectomy. *Acta anaesthesiologica Belgica* 2012, 63(1):43-50.
12. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M, Nishimae K: Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study. *Journal of hepato-biliary-pancreatic surgery* 2009, 16(3):367-371.
13. Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M, Hering W: Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth Analg* 2004, 98(4):1050-1055, table of contents.
14. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, McIntyre LA, Nicole PC, Fergusson DA: Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Canadian journal of anaesthesia = Journal canadien d'anesthésie* 2011, 58(1):22-37.
15. Dogan SD, Ustun FE, Sener EB, Koksall E, Ustun YB, Kaya C, Ozkan F: Effects of lidocaine and esmolol infusions on hemodynamic changes, analgesic requirement, and recovery in laparoscopic cholecystectomy operations. *Rev Bras Anesthesiol* 2017, 66(2):145-150.
16. Lauwick S, Kim DJ, Michelagnoli G, Mistracetti G, Feldman L, Fried G, Carli F: Intraoperative infusion of lidocaine reduces postoperative fentanyl requirements in patients undergoing laparoscopic cholecystectomy. *Canadian journal of anaesthesia* 2008, 55(11):754-760.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine* 2009, 6(7):e1000097.
18. Green S: *Cochrane handbook for systematic reviews of interventions* version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011.
19. Ahn E, Kang H, Choi GJ, Park YH, Yang SY, Kim BG, Choi SW: Intravenous lidocaine for effective pain relief after a laparoscopic colectomy: a prospective, randomized, double-blind, placebo-controlled study. *International surgery* 2015, 100(3):394-401.
20. Harvey KP, Adair JD, Isho M, Robinson R: Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *American journal of surgery* 2009, 198(2):231-236.
21. Kim TH, Kang H, Choi YS, Park JM, Chi KC, Shin HY, Hong JH: Pre- and intraoperative lidocaine injection for preemptive analgesics in laparoscopic gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. *Journal of laparoendoscopic & advanced surgical techniques Part A* 2013, 23(8):663-668.
22. Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, Wu CT: Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery: *British Journal of Anaesthesia*. 97 (5) (pp 640-646), 2006. Date of Publication: November 2006.
23. Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, Mazoit JX, Chauvin M, Bouhassira D, Fletcher D: Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology* 2008, 109(1):118-123.
24. Moeen SM, Moeen AM: Usage of Intravenous Lidocaine Infusion with Enhanced Recovery Pathway in Patients Scheduled for Open Radical Cystectomy: A Randomized Trial. *Pain physician* 2019, 22(2):E71-e80.

25. Staikou C, Avramidou A, Ayiomamitis GD, Vrakas S, Argyra E: Effects of intravenous versus epidural lidocaine infusion on pain intensity and bowel function after major large bowel surgery: a double-blind randomized controlled trial. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014, 18(12):2155-2162.
26. SR I, M OC, AF S, MG B: Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *Journal of cardiothoracic and vascular anesthesia* 1995, 9(5):541-546.
27. L W, C R, S T, W H, M Y, I G, L M, K J, D S, C C: A randomised controlled trial of peri-operative lidocaine infusions for open radical prostatectomy. *Anaesthesia* 2016, 71(4):405-410.
28. Yon JH, Choi GJ, Kang H, Park JM, Yang HS: Intraoperative systemic lidocaine for pre-emptive analgesics in subtotal gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. *Canadian journal of surgery Journal canadien de chirurgie* 2014, 57(3):175-182.
29. Kim HO, Lee SR, Choi WJ, Kim H: Early oral feeding following laparoscopic colorectal cancer surgery. *ANZ journal of surgery* 2014, 84(7-8):539-544.
30. SB G, HA F, RP K, MK P, LJ W, SA M, PD L: Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesthesia and analgesia* 1998, 86(2):235-239.
31. Chen K, Wei P, Zheng Q, Zhou J, Li J: Neuroprotective effects of intravenous lidocaine on early postoperative cognitive dysfunction in elderly patients following spine surgery: *Medical Science Monitor*. 21 (pp 1402-1407), 2015. Date of Publication: 15 May 2015.
32. Kim HJ, Kim WH, Kim G, Kim E, Park MH, Shin BS, Sim WS, Kim CS, Lee YT, Cho HS: A comparison among infusion of lidocaine and dexmedetomidine alone and in combination in subjects undergoing coronary artery bypass graft: a randomized trial. *Contemporary clinical trials* 2014, 39(2):303-309.
33. Lauwick S, Kim DJ, Mistraretti G, Carli F: Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. *British journal of anaesthesia* 2009, 103(2):213-219.
34. Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, Blumenthal JA, Newman MF, Neurologic Outcome Research Group of the Duke Heart C: Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke* 2009, 40(3):880-887.
35. Dewinter G, Coppens S, Van de Velde M, D'Hoore A, Wolhuis A, Cuypers E, Rex S: Quadratus Lumborum Block Versus Perioperative Intravenous Lidocaine for Postoperative Pain Control in Patients Undergoing Laparoscopic Colorectal Surgery: A Prospective, Randomized, Double-blind Controlled Clinical Trial. *Annals of surgery* 2018, 268(5):769-775.
36. Kim JE, Choi JB, Koo BN, Jeong HW, Lee BH, Kim SY: Efficacy of Intravenous Lidocaine During Endoscopic Submucosal Dissection for Gastric Neoplasm: A Randomized, Double-Blind, Controlled Study. *Medicine* 2016, 95(18):e3593.
37. YC C, CL L, TP L, PS Y, MJ C, SP C: Effect of Perioperative Intravenous Lidocaine Infusion on Acute and Chronic Pain after Breast Surgery: A Meta-Analysis of Randomized Controlled Trials. *Pain practice : the official journal of World Institute of Pain* 2017, 17(3):336-343.
38. C C, ED K, I F, S N, D S, HM P, NT V: Meta-analysis of the effect of perioperative intravenous lidocaine on return of gastrointestinal function after colorectal surgery. *Techniques in coloproctology* 2019, 23(1):15-24.
39. M K, H F, T K: Intravenous administration of lidocaine directly acts on spinal dorsal horn and produces analgesic effect: An in vivo patch-clamp analysis. *Scientific reports* 2016, 6(1):26253.
40. B K-M, I B, M F, M K-K, A G, K K, K S, PJ T: Effect of intravenous, perioperative-administrated lidocaine on serum levels of endocannabinoids and related N-acyl ethanolamines in children. *Minerva anesthesiologica* 2019, 18(7):973-980.
41. JS K, N H, S C, S R, JE P, NJL H, C H, JW B, I G, DN B et al: Perioperative Pregabalin and Intraoperative Lidocaine Infusion to Reduce Persistent Neuropathic Pain After Breast Cancer Surgery: A Multicenter, Factorial, Randomized, Controlled Pilot Trial. *The journal of pain : official journal of the American Pain Society* 2019, 20(8):980-993.
42. Dogan SD, Ustun FE, Sener EB, Koksai E, Ustun YB, Kaya C, Ozkan F: Effects of lidocaine and esmolol infusions on hemodynamic changes, analgesic requirement, and recovery in laparoscopic cholecystectomy operations. *Brazilian journal of anesthesiology (Elsevier)* 2016, 66(2):145-150.
43. Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, Joris JL: Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007, 106(1):11-18; discussion 15-16.
44. Kim MH, Kim MS, Lee JH, Kim ST, Lee JR: Intravenously Administered Lidocaine and Magnesium During Thyroid Surgery in Female Patients for Better Quality of Recovery After Anesthesia. *Anesthesia and analgesia* 2018, 127(3):635-641.
45. Bryson GL, Charapov I, Krolczyk G, Taljaard M, Reid D: Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2010, 57(8):759-766.
46. Dale GJ, Phillips S, Falk GL: The analgesic efficacy of intravenous lidocaine infusion after laparoscopic fundoplication: A prospective, randomized, double-blind, placebo-controlled trial: *Local and Regional Anesthesia*. 9 (pp 87-93), 2016. Date of Publication: 02 Dec 2016.

Table

Figures

Table 1 Description of included studies

Studies	Year	Design	Surgery type	Population				Intervention			
				Groups	Sample size	Sex(M/F)	Mean age(y)	Surgery Time(min)	First bolus	Infusion	Duration of infusion
Moeen [24]	2019	RCT	Open Radical Cystectomy	Experiment	54	47/7	60.5	N/A	N/A	2mg/min	4 hours
				Control	57	49/8	60.2	N/A	Saline@same rate and equal volume		
Dewinter [35]	2018	RCT	Laparoscopic Surgery	Experiment	50	27/23	60	146min	1.5mg/kg	1.5mg/kg/h	End of surgery
				Control	25	14/11	60	130min	Saline@same rate and equal volume		
Weinberg [27]	2016	RCT	Open Radical Prostatectomy	Experiment	37	N/A	61.1	N/A	1.5mg/kg	1.5mg/kg/h	To postoperation 4 hour
				Control	38	N/A	60	N/A	Saline@same rate and equal volume		
Kim JE[36]	2016	RCT	Endoscopic submucosal dissection (ESD)	Experiment	30	24/6	65.2	41 min	1.5mg/kg	2mg/kg/h	End of the surgery
				Control	31	21/10	65.0	40 min	Saline@same rate and equal volume		
Staikou[25]	2014	RCT	Laparoscopic Fundoplication	Experiment	20	12/8	73.6	102.25 min	1.5mg/kg	2mg/kg/h	24 hours
				Control	20	16/4	74.4	132 min	Saline@same rate and equal volume		
Ahn[19]	2015	RCT	Laparoscopic Colectomy	Experiment	25	11/14	64.48	216min	1.5mg/kg	2mg/kg/h	End of the surgery
				Control	25	8/17	66.2	204.2min	Saline@same rate and equal volume		
Chen[31]	2015	RCT	Spine Surgery	Experiment	40	23/17	71.3	129.2min	1mg/kg	1.5mg/kg/h	End of the surgery
				Control	40	25/15	71.8	128.3min	Saline@same rate and equal volume		
Kim HJ[32]	2014	RCT	Coronary Artery Bypass Graft	Experiment	36	25/11	66.67	283min	1.5mg/kg	2mg/kg/h	Until the postoperation 24 h
				Control	38	28/10	64.67	247min	No Treatment		
Yon[28]	2014	RCT	Subtotal Gastrectomy	Experiment	17	N/A	60.83	N/A	1.5mg/kg	2mg/kg/h	End of the surgery
				Control	19	N/A	65.67	N/A	Saline@same rate and equal volume		
Kim HO[29]	2014	RCT	Laparoscopic Surgery	Experiment	32	23/9	60.9	N/A	1mg/kg	1mg/kg/h	24h
				Control	36	23/13	60.1	N/A	Saline@same rate and equal volume		
Kim TH[21]	2013	RCT	Laparoscopic Gastrectomy	Experiment	17	11/6	60.17	282min	1.5mg/kg	2mg/kg/h	End of the surgery
				Control	17	10/7	63.0	270.88min	Saline@same rate and equal volume		
Harvey [20]	2009	RCT	Elective Bowel Surgery	Experiment	11	6/5	60	N/A	N/A	60mg/h	24h after surgery
				Control	11	6/5	65	N/A	Saline@same rate and equal volume		
Lauwick [33]	2009	RCT	Laparoscopic Prostatectomy	Experiment	20	N/A	60	258.33	1.5mg/kg	2mg/kg/h during surgery@1mg/kg/h for the PACU 24h	End of the surgery and PACU
				Control	20	N/A	60	238.33	Saline@same rate and equal volume		
Martin [23]	2008	RCT	Total Hip Arthroplasty	Experiment	28	13/15	64	N/A	1.5mg/kg	1.5mg/kg/h	started 30 min before surgical incision and stopped 1h after skin closure
				Control	30	10/20	62	N/A	Saline@same rate and equal volume		
Mathew [34]	2008	RCT	Cardiac Surgery	Experiment	88	N/A	61.7	N/A	1mg/kg	4mg/min for the first hour@2mg/min for the	During 48h

									second hour 1mg/min for the next 46h			
				Control	94	N/A	61.4	N/A	Saline	same rate and equal volume		
Kuo [22]	2006	RCT	Colonic Surgery	Experiment	20	10/10	63	157.8min	2mg/kg	3mg/kg/h	Continuous infusion started 30 min before surgery and the infusions maintained throughout the surgical procedure.	L
				Control	20	12/8	62	150.8min	Saline	same rate and equal volume		
Scott[30]	1998	RCT	Radical Retropubic Prostatectomy	Experiment	20	N/A	64.4	N/A	1.5mg/kg	3mg/min	Until to 60 min after skin closure	L
				Control	20	N/A	64.4	N/A	Saline	same rate and equal volume		
Steven[26]	1995	RCT	Coronary Artery Bypass Grafting	Experiment	44	N/A	62.65	N/A	1.5mg/kg	1.8mg/h	End of surgery to 48 hours in the ICU unless discharged earlier	L
				Control	45	N/A	62.65	N/A	Saline	same rate and equal volume		

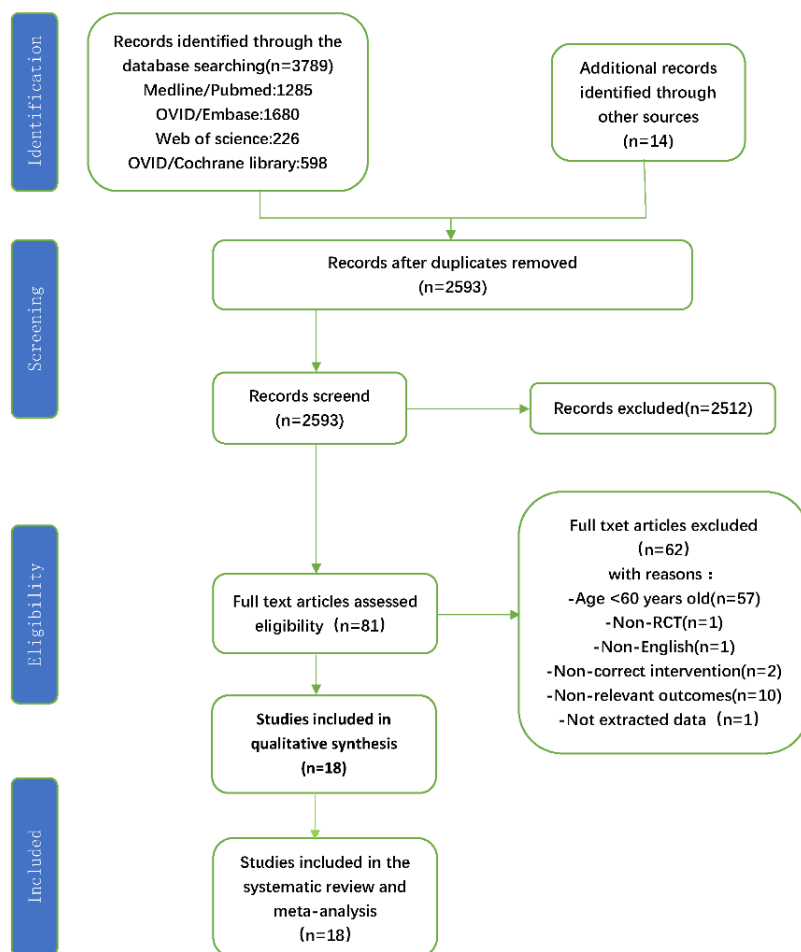


Fig.1 PRISMA flow chart of study selection

Figure 1

PRISMA flow chart of study selection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahn 2015	+	+	?	?	+	+	+
Chen 2015	?	?	?	?	+	+	+
Dewinter 2018	+	?	+	?	+	+	+
Harvey 2009	+	+	+	+	+	+	+
Kim HJ 2014	+	+	+	+	+	+	+
Kim HO 2014	+	?	+	+	+	+	+
Kim JE 2016	+	+	+	+	+	+	+
Kim TH 2013	+	+	+	+	+	+	+
Kuo 2006	+	+	+	+	+	+	+
Lauwick 2009	+	+	+	+	+	+	+
Martin 2008	+	+	+	+	+	+	+
Mathew 2008	+	+	+	?	+	+	+
Moeen 2019	+	?	+	+	+	+	+
Scott 1998	?	+	+	+	+	+	+
Staikou 2014	?	+	+	+	+	?	+
Steven 1995	?	?	?	?	+	+	+
Weinberg 2016	+	+	+	+	+	+	+
Yon 2013	+	+	+	+	+	+	+

Figure 2

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

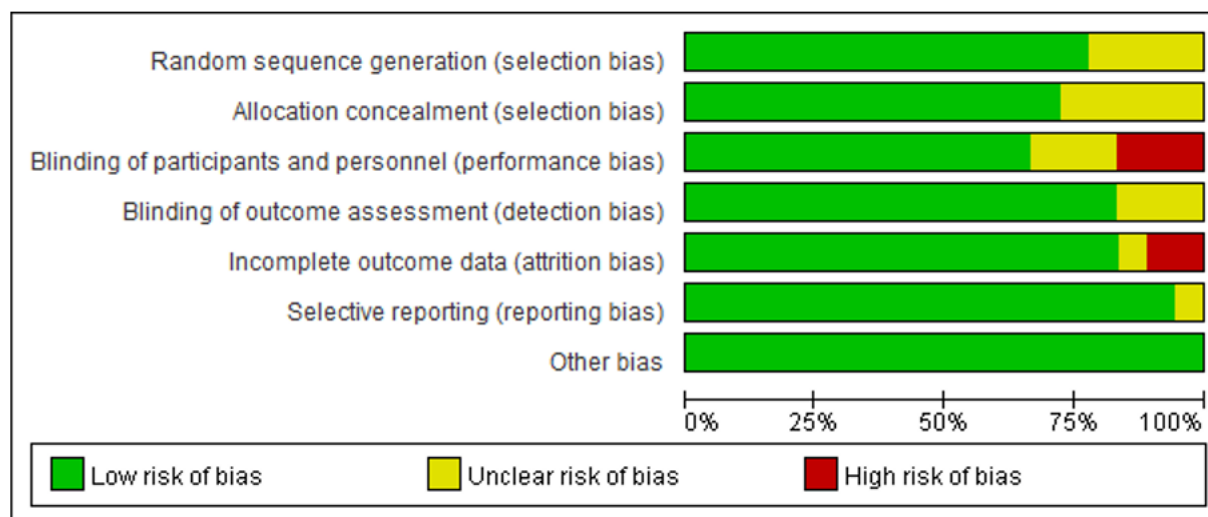


Figure 3

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

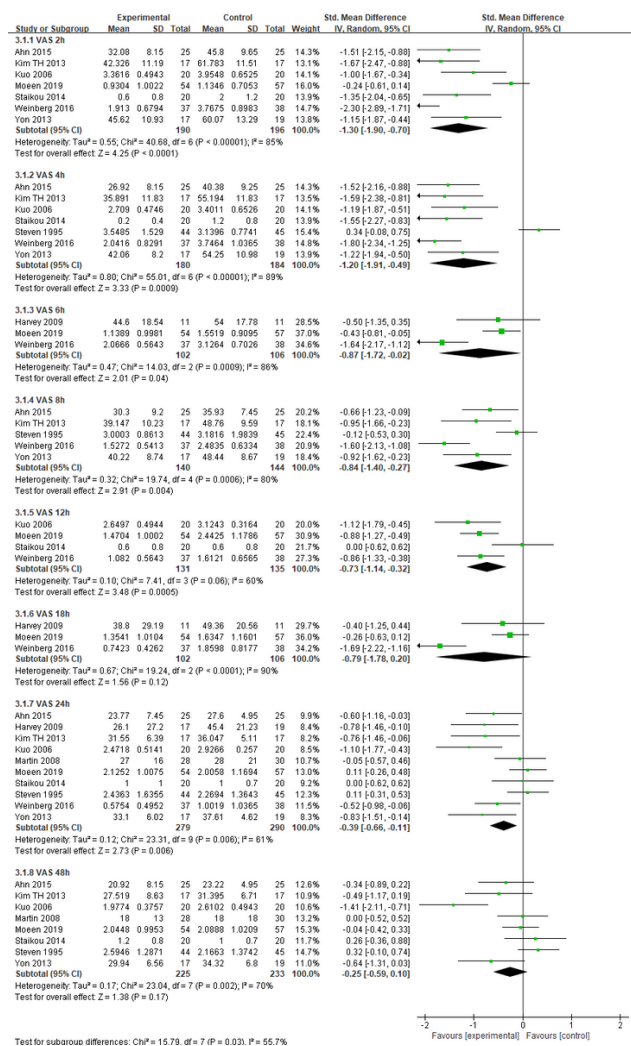


Figure 4

The forest plot for pain score at rest between lidocaine and control groups by time points

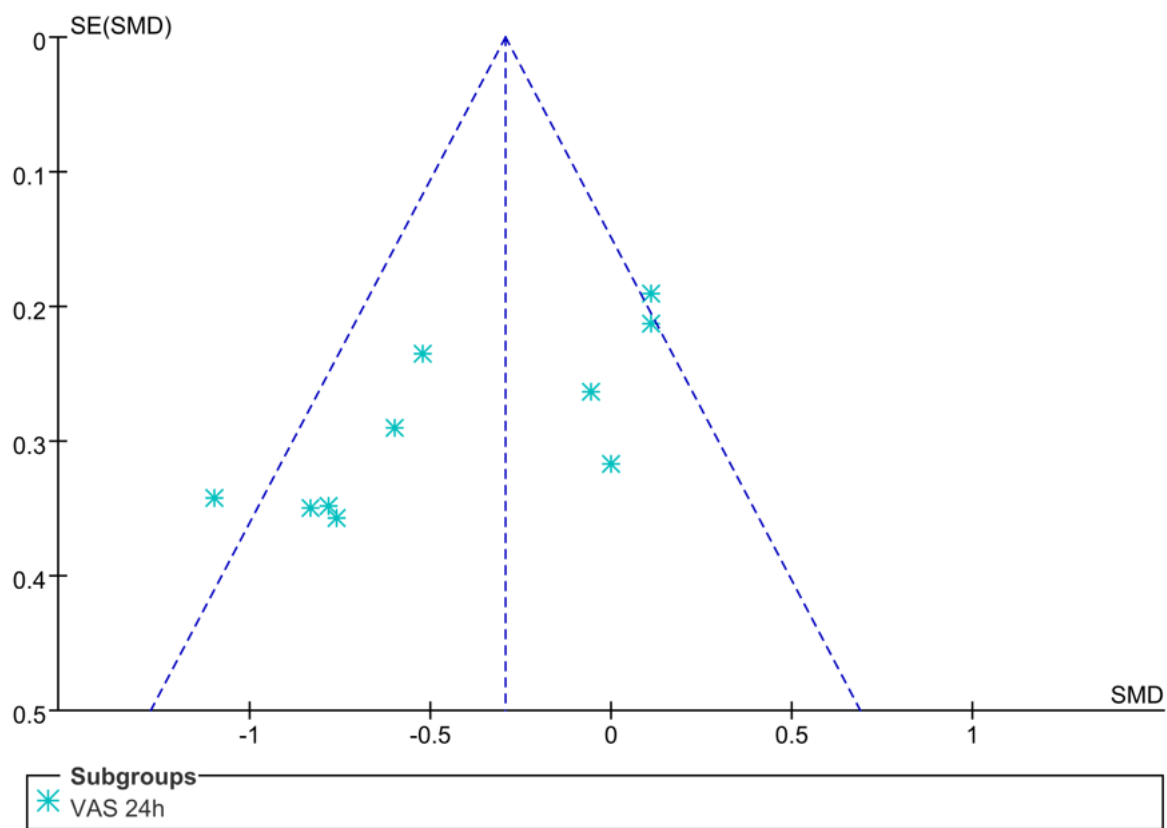


Figure 5

The funnel plot for pain score of 24h at rest between lidocaine and control groups

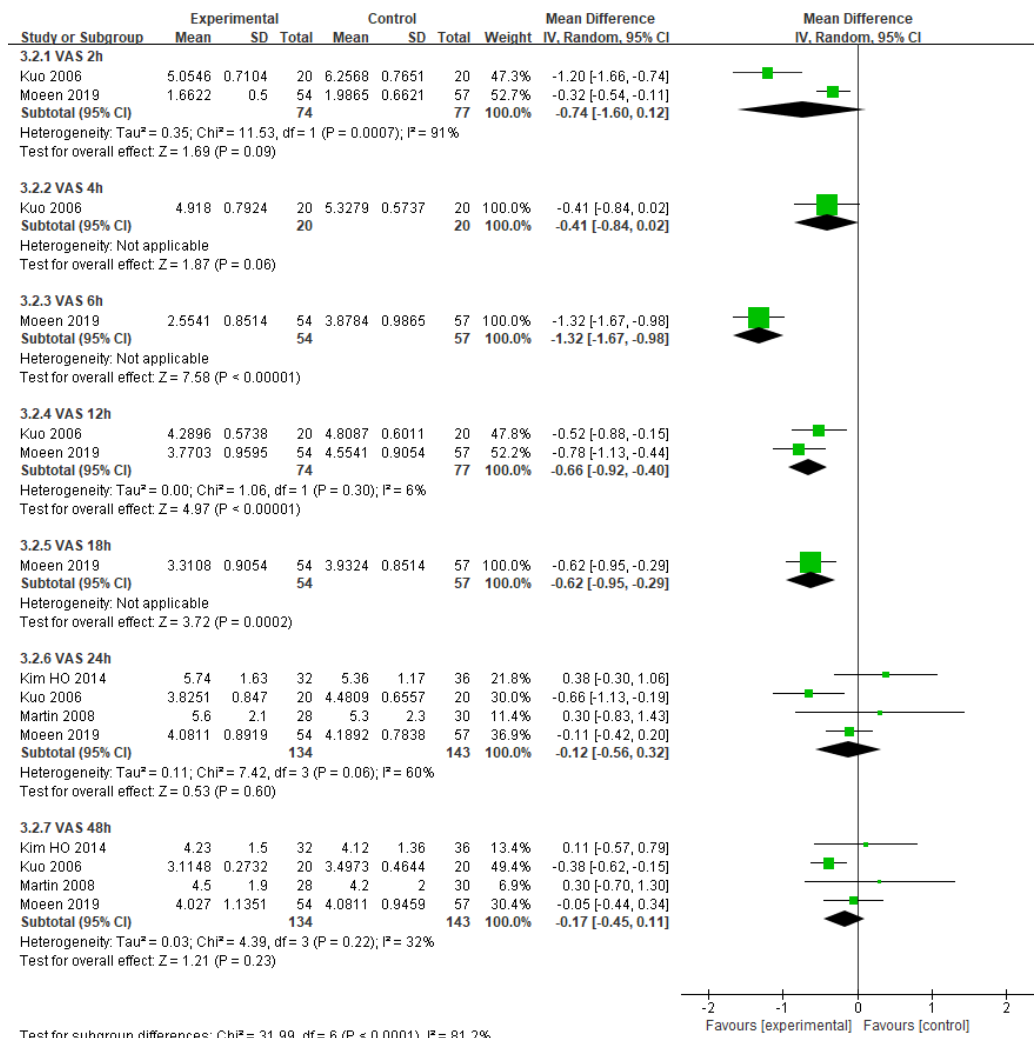


Figure 6

The forest plot for pain score at movement between lidocaine and control groups by difference time points

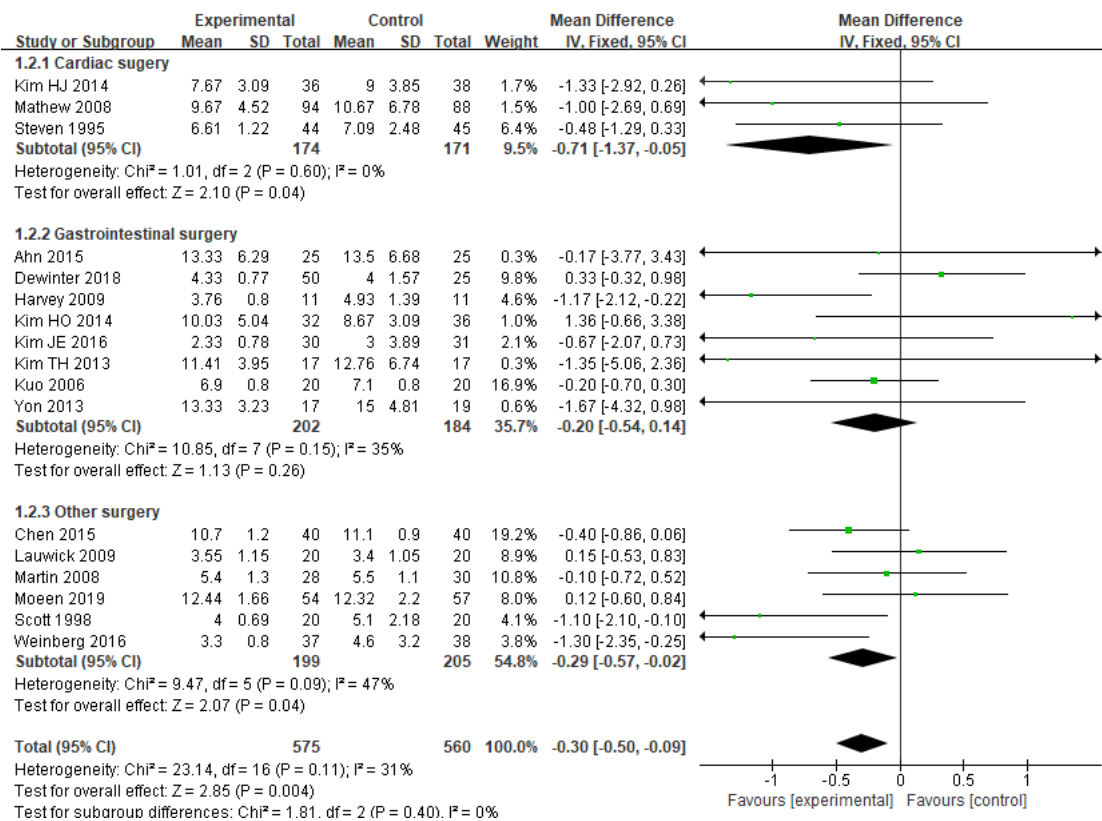


Figure 7

The forest plot for length of hospital stay outcome between lidocaine and control groups by type of surgery

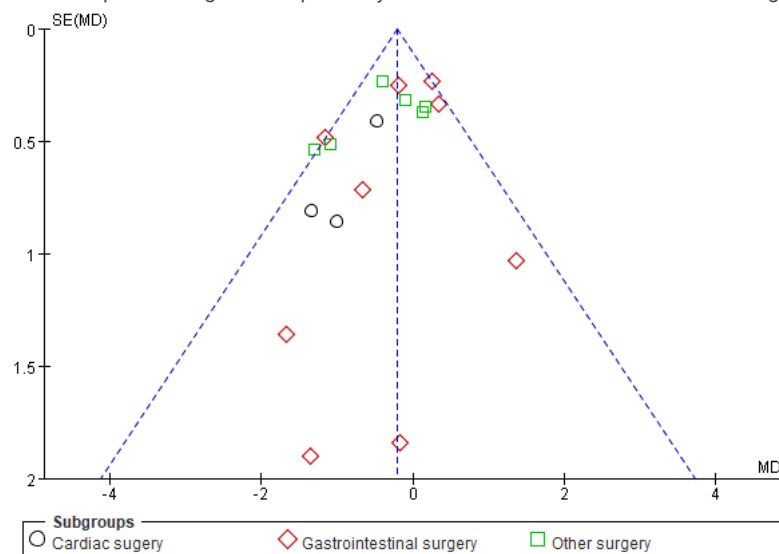


Figure 8

The funnel plot for the length of hospital stay between lidocaine and control groups

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