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Perioperative Systemic Lidocaine for Postoperative Analgesia and Recovery after Laparoscopic Cholecystectomy: systematic review and meta-analyses of randomized controlled trials

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Abstract

Background

Laparoscopic cholecystectomy is one of the commonest operations in the world. Pain is a known significant factor to either delayed postoperative recovery or discharges. Improvement of perioperative outcomes remains huge challenge to perioperative clinicians. The aim of this review was to assess the effects of perioperative intravenous lidocaine infusion compared to placebo on postoperative pain and recovery in adults undergoing laparoscopic cholecystectomy.

Methods

Systematic review of literature conducted using electronic database searched up to November 2017 included Cochrane Central Register of Controlled trials in the Cochrane library, Medline, Embase and Science Citation Index Expanded database to identify relevant studies. Data extracted and critically appraised by two independent authors. In addition, random effects model were applied to calculated pooled results based on degree of heterogeneity.

Results

Five studies were finally included for systematic review and meta-analyses with 300 patients randomly assigned to either perioperative systemic lidocaine or control for postoperative analgesia and recovery after laparoscopic cholecystectomy. Findings were statistically significant in pain intensity in the lidocaine group WMD: -1.18mm (95% CI: -1.65, -0.72); I^2=96% for pain intensity 1 to 4 hours after surgery WMD:-0.49mm (95%CI: -0.84, 0.14); I^2=95% for postoperative pain intensity after 24 hours. Combined data showed reduced opioid consumption in the Lidocaine group compared with the control. WMD:--5.69mg (95% CI: -12.08, 0.70) I^2=91%). In addition, the four studies gave data on opioid consumption intraoperative and in PACU. Three trials provided suitable data on the time to pass first flatus, significantly reduced in the lidocaine group. WMD:-5.14 hours (95%CI: -6.32, -3.96) I^2=27%. Combined data from two studies favours lidocaine group with reduced time to first bowel movement. WMD:-9.10 hours (95% CI: -22.66, 4.46) I^2=86%. PONV occurred in 18% of patients in the lidocaine group and 30% of patients in the control group (OR: 0.48(95%CI: 0.24, 0.96) I^2=0%

Conclusion

Perioperative intravenous lidocaine may be an effective adjunct for postoperative pain management by decreasing

postoperative pain severity, decreasing opioid consumption, less opioid related side effect and facilitate early GI function.

Keyword: Systemic; intravenous; lidocaine; laparoscopic cholecystectomy.

Introduction

Laparoscopic cholecystectomy is one of the commonest operations in the world. Pain is a known significant factor to either delayed postoperative recovery or discharges form the day surgery unit or in-patient ward [1]. Post-operative pain has been considered insufficiently managed in one-half of these patients following laparoscopic cholecystectomy [2]. While opioids remains the maintain stay of post-operative analgesia, their use can be associated with adverse effects including post-operative ileus which can ultimately lead to delayed discharges. Intravenous lidocaine has been shown to improve pain control and enhances early bowel recovery and consequently early discharges [3, 4]. In addition, there are reported studies that shown that systemically administered lidocaine has analgesic, anti-inflammatory and antihyperalgesic effects [5, 6]. Evidence showed that paralytic ileus and post-operative pain are causes of prolonged hospital stay and consequently raised hospital cost [7]. Few meta-analyses has been published to evaluate efficacy of systemic lidocaine for postoperative analgesia and GI recovery following abdominal surgery [8,9,10] but this current study is the first meta-analysis to evaluate available evidences specifically for laparoscopic cholecystectomy. Improvement of perioperative and outcomes remains huge challenge to perioperative clinicians and also a matter of debate. The aim of this review was to assess the effects of perioperative intravenous lidocaine infusion compared to placebo on postoperative pain and recovery in adults undergoing laparoscopic cholecystectomy.

Material and methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) guidelines for systematic review reporting and quality assessment of each trial using Cochrane collaboration tool for assessing risk bias [11]. This design is a systematic review with meta-analysis of RCTs with no restriction on the year of publication or language. This review included RCTs comparing perioperative systemic lidocaine with placebo for postoperative analgesia and recovery after laparoscopic cholecystectomy. Inclusion criteria were RCTs, investigating perioperative systemic lidocaine in laparoscopic cholecystectomy in adults 18 years of age or older. The continuous IV lidocaine must have been started intraopertively with or without bolus prior to incision and continued until the end of surgery, trials that reported postoperative pain outcomes, opioid consumption and time to first flatus and defecation.

Exclusion criteria were other abdominal surgeries aside laparoscopic cholecystectomy, observational studies, conference articles, abstracts and non-randomised studies.

The primary outcome measures analysed were pain score, post-operative ileus and functional G.I recovery (time of defecation, time of first flatus or first bowel motion or sounds. Secondary outcomes included length of hospital stay and opioid related side effects of nausea and vomiting.

Search methods

Electronic database searched up to November 2017 included Cochrane Central Register of Controlled trials in the Cochrane library, Medline (1950 to November 2017), Embase (1980 to November 2017), and Science Citation Index Expanded database (1970 to November 2017).

Key words were mapped to Medline medical subject Heading (MESH) terms and searched for as text items.

RCTs filter was further used to sieve out non-randomised studies from Medline and Embase. Hand searches of references of cited journal conducted to further identify potential eligible articles for this review.

Data collection

Required outcome data collected by two reviewers who independently made the data extraction after reading the full text of all the included studies. Publication data, author, number of patients, interventions, study design and primary outcomes were recorded in this systematic review. The data were further synthesised into comprehensive summary of randomised trials table comparing both treatment outcomes. Authors were contacted by email for missing data. The primary end points of this review included pain scores 4 and 24 hours after surgery, cumulative opioid consumption, time to first flatus and time of first bowel movement or defecation and secondary end points included length of hospital stay and opioid related side effects of nausea and vomiting. The visual analogue scale (VAS 0-100mm) was employed as a measure of intensity of pain (0= no pain, 100= worst pain ever). Opioids analgesics were converted to morphine equivalent doses in milligrams [12]. Secondary ends included length of hospital stay and opioid related side effects of nausea and vomiting.

Assessment of risk of bias in includes studies

The assessment of risk of bias was done on trials using the six main components of the Cochrane collaboration format [11] tool. Sequence generation, allocation concealment of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias were included.

Statistical Analysis

The software package Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, (Denmark) was used for data analysis. For continuous outcomes weighted mean differences (WMDs) with 95% confidence interval (CI) was calculated for the meta-analysis. For data with zero events, risk difference was calculated and used for the mortality results. For continuous outcomes, the mean difference with 95% CI was used, and the estimated result was used for the meta-analysis. When mean and SD were not given , they were estimated from median and SE or CI, or from interquartile range if data distribution not skewed.Dichotomous data were analysed by the use of relative risk (RR) with 95% CI. If statistical heterogeneity existed, the random-effects model was reported. Heterogeneity was explored using χ^2 test to provide an indication for between-study, heterogeneity was considered significant when $I^2 \geq 50\%$ or when X- square test resulted in $P < 0.05$. Statistical heterogeneity for each pooled summary was estimated using I^2 statistics presented as a percentage. A careful review of studies was conducted to identify any findings of significant heterogeneity. A funnel plot of trials undergoing meta-analysis was used to determine if any publication bias existed in outcomes involving data from the trials.

Validity Assessment

Validity assessment was carried out according to risk of bias guidelines specified in the *Cochrane Handbook for Systematic Reviews of Interventions* by Akhigbe T and Hraishawi I the differences resolved through discussion. The risks of bias including 6 criteria were analysed: random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases. Validity assessment scoring and weighting tools were not used as per Cochrane recommendations. In surgical trials, blinding of participants and personnel is difficult and unfeasible and was not considered for this review.

Results

The literature search identified 1928 studies, including 1227 in Medline, 626 in Embase and 43 in the Cochrane

Central Register of Controlled Trial. Internet-based registry search yielded 15, journal search yielded eight studies, conference preceding five and references five After further screening by the investigative team 1903 out of 1928 studies were extracted for full text review, and 20 out of these studies were excluded because they were non-randomised studies. Five studies were finally included for systematic review and meta-analyses. There were 300 patients randomly assigned to either perioperative systemic lidocaine or placebo (control) for postoperative analgesia and recovery after laparoscopic cholecystectomy[Fig 1]

Study Characteristics

Extensive database search identified five RCTs [13, 14, 15, 16, 17] with 281 patients randomly assigned to either perioperative systemic lidocaine use or placebo for postoperative analgesia and recovery after laparoscopic cholecystectomy [Table 1]

Critical Appraisal

All the five peer-reviewed RCTs were small with patient's number between 25 and 80. Methodological quality was assessed Jadad score. Four of the studies scored high Jadad score [23] [Table 2]

Assessment of risks of bias of RCTs

The assessment of risk of bias was done on the RCTs using the six main component Cochrane tool. Sequence generation, allocation concealment, blinding of participants, personnel and outcome assessor, incomplete outcome data, selective outcome reporting and other sources of bias were included. Details of methodological assessment showed in Figure 2. All trials include were randomised, double blind and placebo-controlled clinical trial.

Meta-analysis outcomes of RCTs

Post-operative Pain Intensity; A total of five RCTs (13-17) evaluated pain intensity after laparoscopic surgery, all the five trials reported VAS pain scores at 4 hours and at 24 hours. Both findings showed statistically significant in pain intensity in the lidocaine group. WMD: -1.18mm (95% CI: -1.65, -0.72); I^2 =96% for pain intensity 1 to 4 hours after surgery. WMD:-0.49mm (95%CI: -0.84, 0.14); I2=95% for postoperative pain intensity after 24 hours.

Cumulative Opioid Consumption; Four studies (13, 14, 17, 17) presented data on total opioid consumption

From the end of surgery to 48 hours after surgery. Combined data showed reduced opioid consumption in the Lidocaine group compared with the control. WMD:--5.69mg (95% CI: -12.08, 0.70); I^2 =91%). In addition, the four studies gave data on opioid consumption intraoperative and in PACU.

Time to First Flatus: Three trials (14, 15, 17) provided suitable data on the time to pass first flatus, significantly reduced in the lidocaine group. WMD:-5.14 hours (95%CI: -6.32, -3.96) I^2=27%

Time to First Bowel Movement: Combined data from two studies (16, 17) favours lidocaine group with reduced time to first bowel movement. WMD:-9.10hours (95% CI: -22.66, 4.46) I2=86%

Opioid-Related Side Effects: Four trials (14-17) reported incidence of postoperative nausea and vomiting. PONV occurred in 18% of patients in the lidocaine group and 30% of patients in the control group (OR: 0.48(95%CI: 0.24, 0.96) I^2=0%.

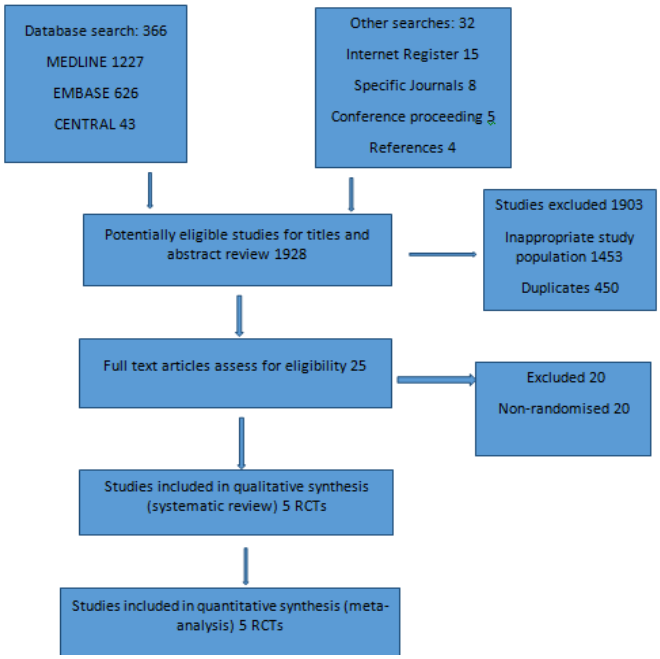

Figure 1: Flow diagram of study search

Study/ Year	Study Design	Lidocaine /control	Intervention	Outcomes / End points
Song 2017	RCT	36/35	IV bolus 1.5mg/kg at induction then continued 2mg/kg/hr until the end of surgery	Pain score, opioid consumption, time to first flatus
Yang 2014	RCT	26/24	IV bolus 1.5mg/kg 2mins before induction then continued 2mg/kg/hr until the end of surgery	Pain score , time of first flatus, length of hospital stay
Saadawy 2010	RCT	40/40	IV bolus (2mg/kg) 15 min before surgery followed by continuous infusion	Pain score, opioid consumption, time to first flatus
Lauwick 2008	RCT	25/24	IV bolus (1.5mg/kg) at induction of anaesthesia followed by continued infusion (2mg/kg/hr) until the end of surgery	Pain score, opioid consumption, length of PACU stay
Wu 2005	RCT	25/25	IV infusion (3mg/kg/h) started 30mins before surgery and continued throughout surgery	Pain score, opioid consumption, time to first flatus

Table 1 Study Characteristics

Study/ Year	Setting	Total	Randomization	Blinding	Attrition factor	Concealment Allocation	Intention to treat
Song 2017	Single centre	5	2	2	1	Adequate	Yes
Yang 2014	Single centre	4	2	2	1	Adequate	Yes
Saadawy 2010	Single centre	4	1	2	1	Not clear	Yes
Lauwick 2008	Single centre	4	1	2	1	Not clear	Yes
Wu 2005	Single centre	1	0	0	1	Not clear	Yes

Table 2: Critical Appraisal (Jadad Score)

Outcomes	Number of RCTs	Number of patients	Statistical method	Effect estimate
Postoperative Opioid Consumption	4	269	Mean Difference (IV, Random, 95% CI	-5.69 [-12.08, 0.70]
Time to pass first flatus (hours)	5	201	Mean Difference (IV, Random, 95% CI	-5.14 [-6.32, -3.96]
Time to first bowel moment or sound	2	121	Mean Difference (IV, Random, 95% CI	9.10 [-22.66, 4.46]
Pain Score (VAS 0-10, 1 to 4 hours)	5	300	Mean Difference (IV, Random, 95% CI	1.18 [-1.65, -0.72]
Pain Score(VAS 0-10, 24hours)	5	300	Mean Difference (IV, Random, 95% CI	-0.49 [-0.83, -0.14]

PONV 0-24hr, -48hr, -72hr	4	215	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.96]
Length of hospital stay (days)	1	50	Mean Difference (IV, Random, 95% CI	-0.20 [-0.53, 0.13]
Intraoperative opioid consumption	2	129	Mean Difference (IV, Random, 95% CI	-9.43 [-11.70, -7.16]

Table 3: Outcome of meta-analysis

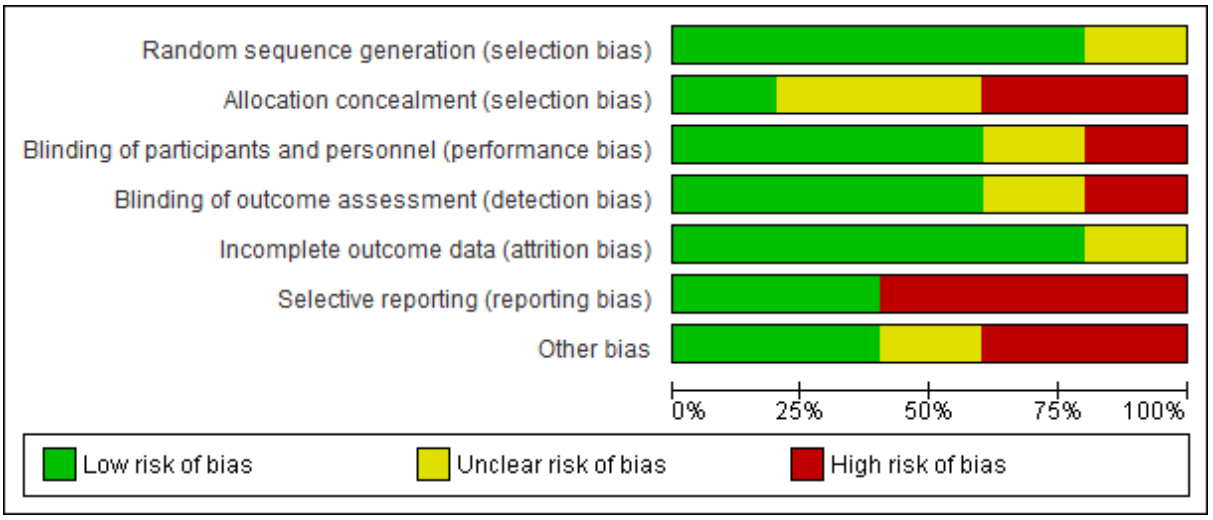

Figure 2: Risk of Bias graph

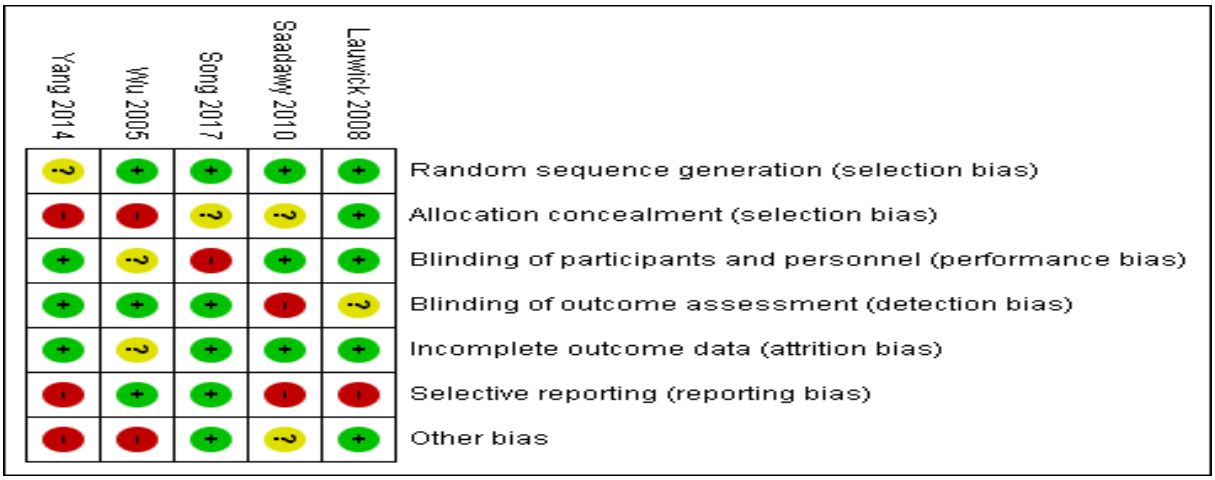

Figure 3: Risk of bias summary

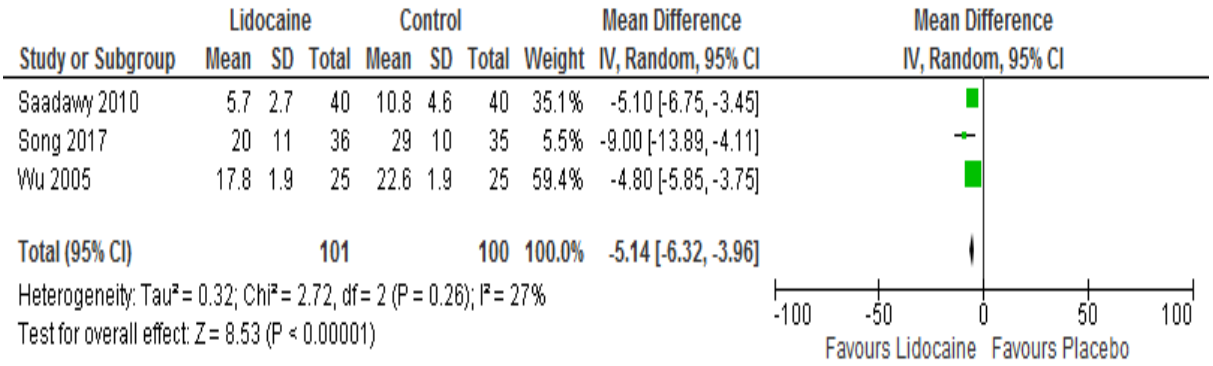

Figure 4: Time to First Fatus (hours)

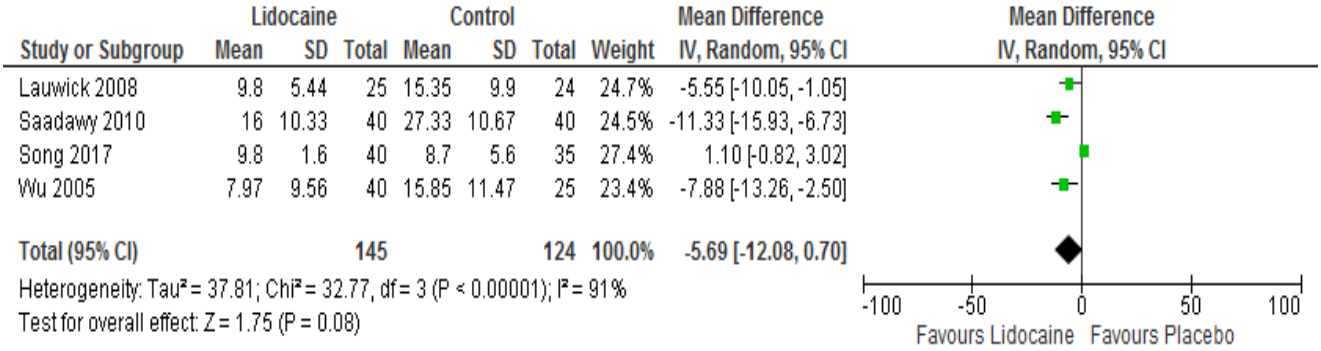

Figure 5: Cumulative postoperative opioid consumption (mg)

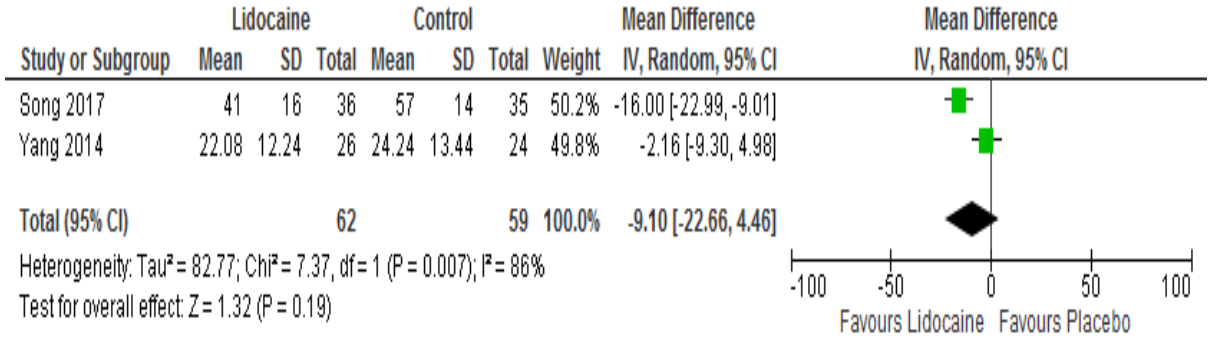

Figure 6: Time to first bowel movement or sound

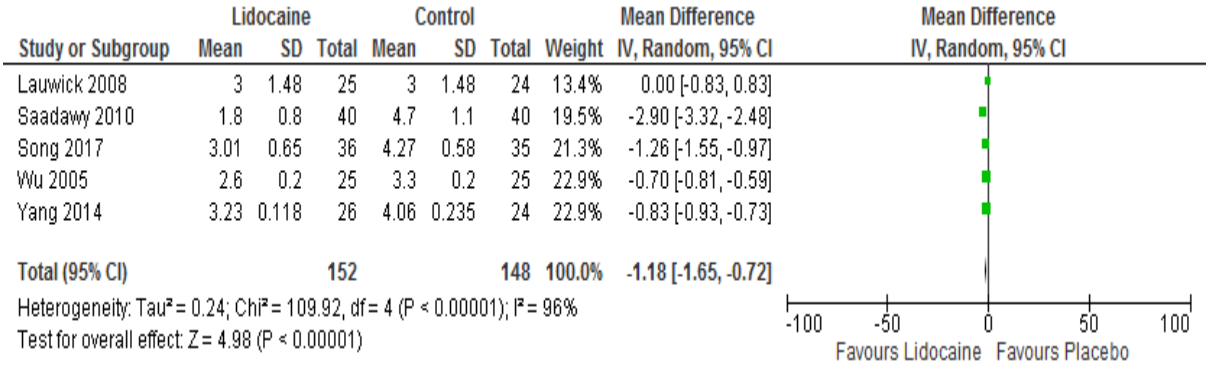

Figure 7: Pain score (VAS 0-10, 1to 4 hours)

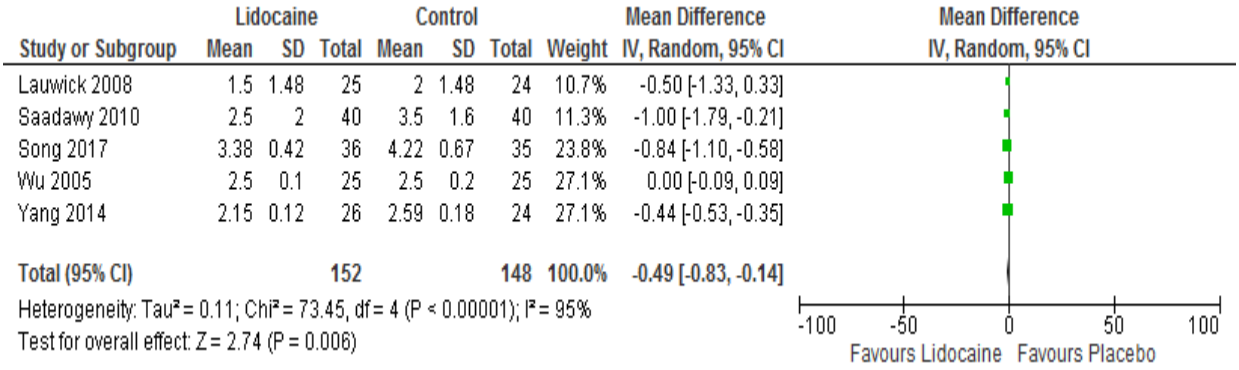

Figure 8: Pain score VAS 0-10, 24hr

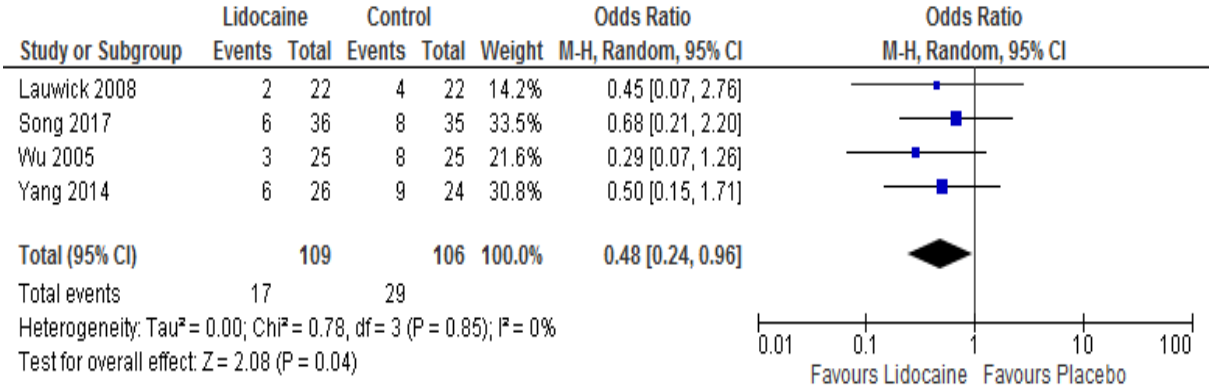

Figure 9: PONV 0-24hr, -48hr, 72hr

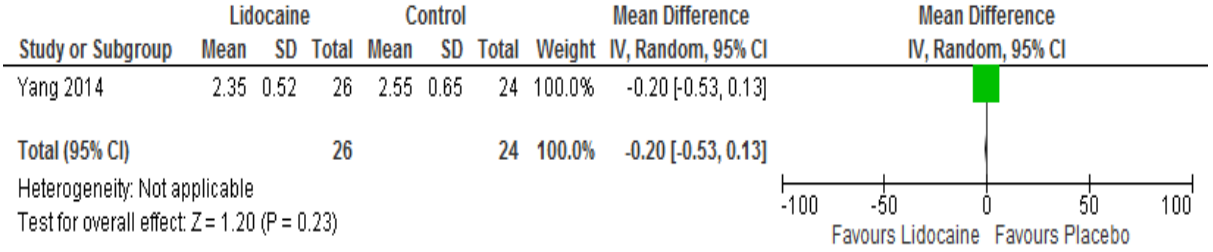

Figure 10: Length of hospital stay

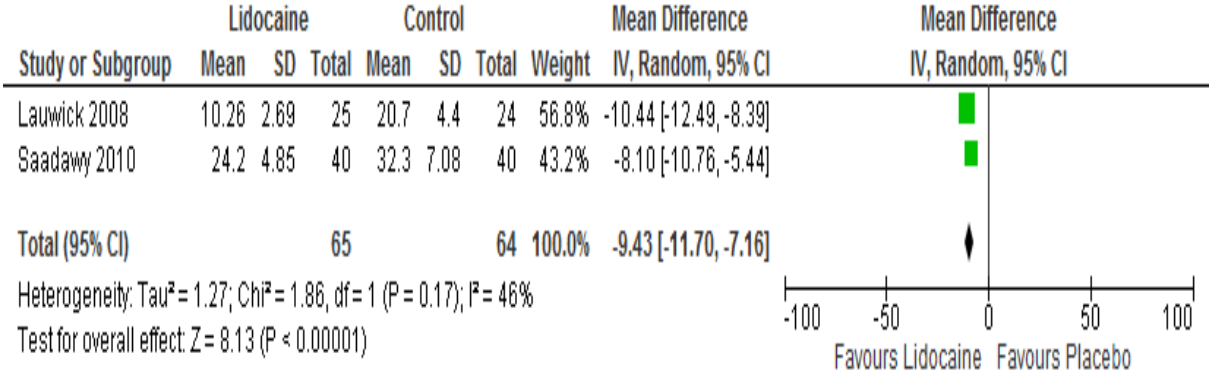

Figure 11: Intraoperative opioid consumption

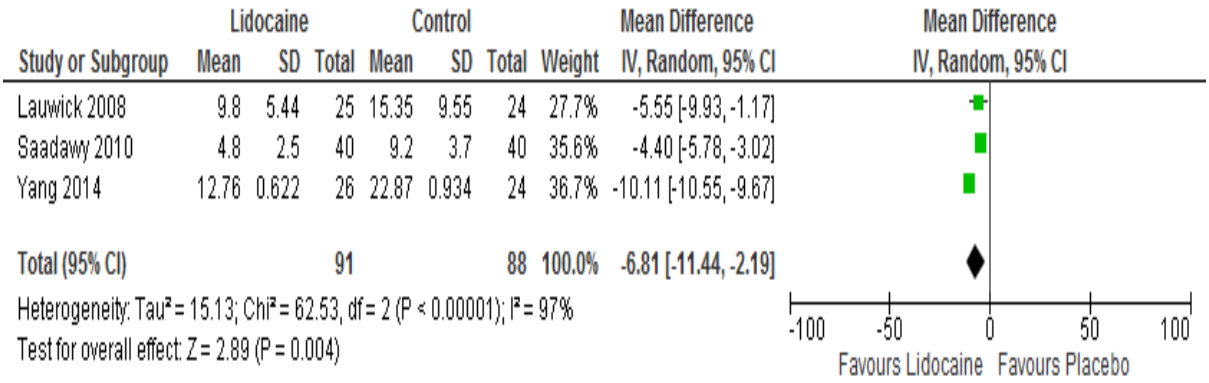

Figure 8: Postoperative opioid consumption (PACU)

Discussion

The most important finding of this study is that systemic lidocaine can significantly reduce post-operative pain scores and opioid consumption. This meta-analysis demonstrates that perioperative intravenous lidocaine is an effective adjunct for management of pain after laparoscopic cholecystectomy hence improves postoperative recovery outcomes. Postoperative pain severity was reduced, urgent return of bowel function compared to control. Improvement in pain scores with systemic lidocaine in other abdominal surgery has been reported about three previous meta-analyses [8, 9,10] just as shown in our meta-analysis. Multimodal analgesia techniques for acute pain management improves better postoperative outcomes and facilitate early convalescence [18]. Our study also revealed that patients lower opioid amount during the postoperative phase following administration of systemic lidocaine.

However, the benefits of lidocaine for pain management in abdominal surgery (including laparoscopic cholecystectomy) remain controversial. Study by McCarthy et al[24] revealed that patients who received lidocaine infusion had lower pain scores, and decreased intraoperative anaesthetic requirements, as well as faster return of bowel function and decreased length of hospital stay. On the contrary, Herroeder et al [25] found that there was no significant difference in postoperative pain ratings for patients undergoing colorectal surgery. Further RCTs will be required to explore dose-response effect and analysis of systemic lidocaine in abdominal surgery.

The mechanism of analgesic effect of intravenous lidocaine remains unclear but one study reported selective suppression of pain transmission through the spinal cord[19]. In addition, intravenous lidocaine has been found to attenuate the production of IL-8, which is the first endogenous mediator for evoking hyperalgesia involving sympathetic nervous system [20].

This study showed that intravenous lidocaine facilitates early return of bowel function. This is achieved by lidocaine blockade of afferent or efferent sympathetic inhibitory spinal and prevertebral reflexes [21] and by reducing the inflammatory response [22] providing opioid sparing effect. Naito et al [22x] reports higher levels of inflammatory mediators in major abdominal surgery compared with less extensive operation. Hence, intravenous lidocaine was more preferable for reducing inflammation during surgery.

One major postoperative complication following additional opioid was nausea and vomiting which could also be related to systemic use of morphine. Four studies in our met analysis reported nausea and vomiting with overall incidence of 17/109 in the lidocaine groups compared 29/ 106 in control groups, though statistically

insignificant [Fig 9], large sample sizes of high-quality studies are, therefore, needed.

Our meta-analysis is the first specifically evaluating intravenous lidocaine in laparoscopic cholecystectomy, we have included five RCTs with high Jadah score [Table 2] hence this is a reliable result. However, there are several limitations of this review including limited number of RCTs with limited number of patients, variability of lidocaine regimen, short duration of follow up and outcomes measures were inconsistent across all studies.

Conclusion

This systematic review suggests that perioperative intravenous lidocaine is an effective adjunct for management of pain following laparoscopic cholecystectomy with most commonly used regimen of IV bolus of 1.5mg/kg followed by an infusion of 1.5mg/kg/hr or 2mg/kg/hr. Perioperative intravenous lidocaine may be an effective adjunct for postoperative pain management by decreasing postoperative pain severity, decreasing opioid consumption, less opioid related side effect and facilitate early GI function.

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Appendix B: The Jadad Scale

B1. Scoring

The articles received a score of 1 for each of the following criteria:

1. Was the study described as randomized (this includes the use of word such as randomly, random and randomization)?

2. Was the study described as double blind?

3. Was there a description of withdrawal and dropouts?

Give 1 additional point if:

For question 1, the method to generate the sequence of randomization was described and it was appropriate

And/or for question 2, the method of double blinding was described and it was appropriate.

Deduct 1 point if:

For question 1, the method to generate the sequence for randomization was described and it was inappropriate

and/or for question 2, the study was described as double blind but the method for double blinding was inappropriate.

B2. Guidelines for assessment

B.2.1. Randomization

A method to general the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be regarded as appropriate.

B.2.2. Double blinding

A study must be regarded as double blind if the term double blind is used. The method will be regarded as appropriate if it is clear that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if (in the absence of such a statement) the use of active placebos, identical placebos, or dummies is mentioned.

B.2.3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.