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Review Article

CLINICAL PRACTICE

Impact of intravenous and topical lidocaine on clinical outcomes in patients receiving propofol for gastrointestinal endoscopic procedures: a meta-analysis of randomised controlled trials

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Abstract

Background: The efficacy of i.v. or topical lidocaine as an anaesthesia adjunct in improving clinical outcomes in patients receiving gastrointestinal endoscopic procedures under propofol sedation remains unclear.
Methods: Electronic databases (MEDLINE, EMBASE, and Cochrane Library) were searched for RCTs comparing the clinical outcomes with or without lidocaine application (i.v. or topical) in patients receiving propofol for gastrointestinal endoscopic procedures from inception to 29 March 2021. The primary outcome was propofol dosage, while secondary outcomes included procedure time, recovery time, adverse events (e.g. oxygen desaturation), post-procedural pain, and levels of endoscopist and patient satisfaction.
Results: Twelve trials (1707 patients) published between 2011 and 2020 demonstrated that addition of i.v. (n=7) or topical (n=5) lidocaine to propofol sedation decreased the level of post-procedural pain (standardised mean difference [SMD]= -0.47, 95% confidence interval [CI]: -0.8 to -0.14), risks of gag events (risk ratio [RR]=0.51, 95% CI: 0.35–0.75), and involuntary movement (RR=0.4, 95% CI: 0.16–0.96). Subgroup analysis demonstrated that only i.v. lidocaine reduced propofol dosage required for gastrointestinal endoscopic procedures (SMD=-0.83, 95% CI: -1.19 to -0.47), increased endoscopist satisfaction (SMD=0.75, 95% CI: 0.21–1.29), and shortened the recovery time (SMD=-0.83, 95% CI: -1.45 to -0.21). Intravenous or topical lidocaine did not affect the incidence of oxygen desaturation (RR=0.72, 95% CI: 0.41–1.24) or arterial hypotension (RR=0.6, 95% CI: 0.22–1.65) and procedure time (SMD=0.21, 95% CI: -0.09 to 0.51).
Conclusion: This meta-analysis demonstrated that i.v. or topical lidocaine appears safe to use and may be of benefit for improving propofol sedation in patients undergoing gastrointestinal endoscopic procedures. Further large-scale trials are warranted to support our findings.

Keywords: anaesthsia; colonoscopy; gastrointestinal endoscopic procedure; intravenous lidocaine; propofol; sedation; topical lidocaine

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Editor's key points

- Despite wide acceptance of combination regimens to minimise dose-dependent propofol-related adverse events, there is no pooled evidence supporting the benefits of i.v. or topical lidocaine in patients receiving gastrointestinal endoscopic procedures.
- This meta-analysis of 12 trials (1707 participants) demonstrated that the addition of i.v. or topical lidocaine to the propofol sedation regimen during gastrointestinal endoscopic procedures could decrease the level of post-procedural pain, risk of gag events, and involuntary movement without significant impacts on haemodynamic and respiratory profiles.
- Subgroup analysis showed that only i.v. lidocaine reduced propofol dosage, increased endoscopist satisfaction and shortened recovery time without adversely affecting procedure time.

Gastrointestinal endoscopic procedures (GEPs) are the gold standard for both the assessment and treatment of various gastrointestinal diseases.[1] Current practice guidelines recommend the application of sedation during the procedures for alleviating the associated physical and emotional stress, thereby improving the examination outcomes and diminishing the patients' traumatic memories.[1] Among various sedatives available (e.g. benzodiazepines) for GEPs,[2] propofol has been gaining popularity because of its unique pharmacokinetic advantages of fast onset and rapid recovery.[3–5] Nevertheless, clinical concerns remain about its use. For instance, a relatively large dose of propofol may elevate the risk of respiratory depression or hypotension in patients with pre-existing cardiopulmonary diseases or advanced age.[6–9]

Larger doses of propofol are usually required to attain an adequate depth of sedation for GEPs because of its weak analgesic properties.[10] Adjunctive agents including opioid, benzodiazepine, or dexmedetomidine[1,11–13] could be combined to increase patient satisfaction, decrease the hypnotic dose of propofol, and reduce the risk of oversedation.[14,15] Consistently, previous studies proposed the use of combination regimens for minimising the dose-dependent propofol-related adverse events.[16,17] However, the use of opioid or benzodiazepine may be associated with the risk of post-procedural neurocognitive dysfunction[18–20] unfavourable for outpatient procedures. In this aspect, i.v. or topical lidocaine could be another potentially useful adjunct to propofol sedation for GEPs. A previous study demonstrated that i.v. lidocaine could reduce propofol requirements by 50%, post-colonoscopy pain, and fatigue after colonoscopy.[21] In addition, topical lidocaine could improve patients' tolerance of upper gastrointestinal endoscopy.[22,23] To provide pooled evidence for clinical practice, this meta-analysis aimed at investigating the therapeutic benefits of i.v. or topical lidocaine in patients receiving propofol for various GEPs.

Methods

Study design

Our meta-analysis was registered with The International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42021232648). This study complies with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.

Search strategy

Two authors (KCH and MY) independently searched the Medline, Cochrane Library, and EMBASE databases from inception to March 29, 2021. The Boolean operator 'OR' was used to cover similar concepts while 'AND' was used to intersect different concepts. The following keywords were applied to the search for relevant records: 'sedative endoscopy', 'gastroscop*', 'colonoscop*', 'endoscopic retrograde cholangiopancreatography', 'ERCP', 'endoscopy', 'endoscopic submucosal dissection', 'esophagogastroduodenoscopy', 'upper gastrointestinal endoscopy', 'topical pharyngeal anesthesia', 'lidocaine*', 'topical anesthesia', 'lignocaine*', 'xylocaine*'. Subject headings (i.e. MeSH terms in PubMed and Cochrane Library and Emtree terms in Embase) were also used in the searching process. The detailed search strategy is available in Supplementary Table S1. Additional studies were identified through reviewing the reference lists of the included studies.

Eligibility criteria

All trials were selected by two reviewers (JYC and LKW) based on meeting all of the following population, intervention, comparator and outcomes (PICO) criteria: (a) Population: patients receiving propofol for GEPs; (b) Intervention: administration of i.v. or topical lidocaine; (c) Comparison: placebo or no intervention; (d) Outcome: propofol requirement and other sedation outcomes. Only RCTs with availability of full text of the article were included. We excluded studies in which topical lidocaine was not applied over the laryngeal area and those in which i.v. lidocaine was used for the purpose of alleviating propofol-associated injection pain. We did not exclude studies based on geographical regions or languages. A third reviewer (YTL or CKS) was consulted for discussion and reaching consensus in case of a discrepancy in study selection.

Primary and secondary outcomes

The primary outcome was the dosage of propofol required for sedation, whereas the secondary outcomes included the procedural time, recovery time, pain or discomfort score, satisfaction of patients or endoscopists, and the incidence of oxygen desaturation, hypotension, and other adverse events (e.g. gag event or vomiting). In addition, subgroup analyses were conducted for all outcomes according to the routes of administration (i.e. i.v. *vs* topical) if applicable. Furthermore, the impacts of different confounding factors on the primary outcome (i.e. propofol dosage) were further evaluated by subgroup analyses including whether adjuvants were used, the use of lidocaine infusion after lidocaine bolus, and the nature of the endoscopic procedures (i.e. upper or lower GEPs).

Risk of bias assessment

The methodological quality of the included RCTs was examined by two reviewers (YJC and YPC) with the Cochrane Risk of Bias Tool.[24] Disagreements were settled through discussion with a third reviewer (YTL or CKS) until a consensus was reached. The potential risk of bias of the included studies was rated by assigning a risk score of 'low', 'high', or 'unclear' to each trial.

Data extraction

Datasets were extracted by two independent reviewers (KML and CNH) from each eligible trial. Two reviewers (KML and CNH) independently performed the extraction of data that included: primary author, year of publication, procedures, study setting, patient characteristics, sample size, dosage of lidocaine, and sedative outcomes (e.g. episode of desaturation). Disagreements were resolved through the involvement of a third author (YTL or CKS) until a consensus was reached. On encountering studies with unclear primary or secondary outcomes, we contacted the authors for further details.

Statistical analysis

For analysis of dichotomous outcomes, a random effects model was applied to calculate the risk ratios (RRs) with 95% confidence intervals (CIs). The Mantel–Haenszel method was used to pool dichotomous data and to compute pooled RRs with 95% CIs. For continuous data, the mean difference was used for grouping trials adopting the same outcome parameters, while the standardised mean difference (SMD) was used to combine trials that utilised different parameters to measure the same outcome. I^2 statistics were applied to quantify the degree of statistical heterogeneity (low: 0–50%; moderate: 51–75%, high: 75–100%). The random effects model was utilised for all meta-analyses given the expected heterogeneity among different studies. When three or more studies reported on a particular outcome, sensitivity analyses were performed by omitting the studies from the meta-analysis one at a time to explore the potential impact of a single trial on the overall results. When 10 or more studies reported on a particular outcome, we assessed the potential publication bias by visual inspection of the funnel plot produced by plotting the standard error against the log odds ratio of studies. The significance level was set at 0.05 for all analyses. Cochrane Review Manager (RevMan 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for data synthesis.

Results

Study selection

The systematic search of the Medline, Embase, and Cochrane library yielded 864 records (Fig. 1). After removing 377 duplicates, the titles and abstracts of the remaining 487 records were screened for the appropriateness of their PICO (Population, Intervention, Comparator and Outcomes) questions and

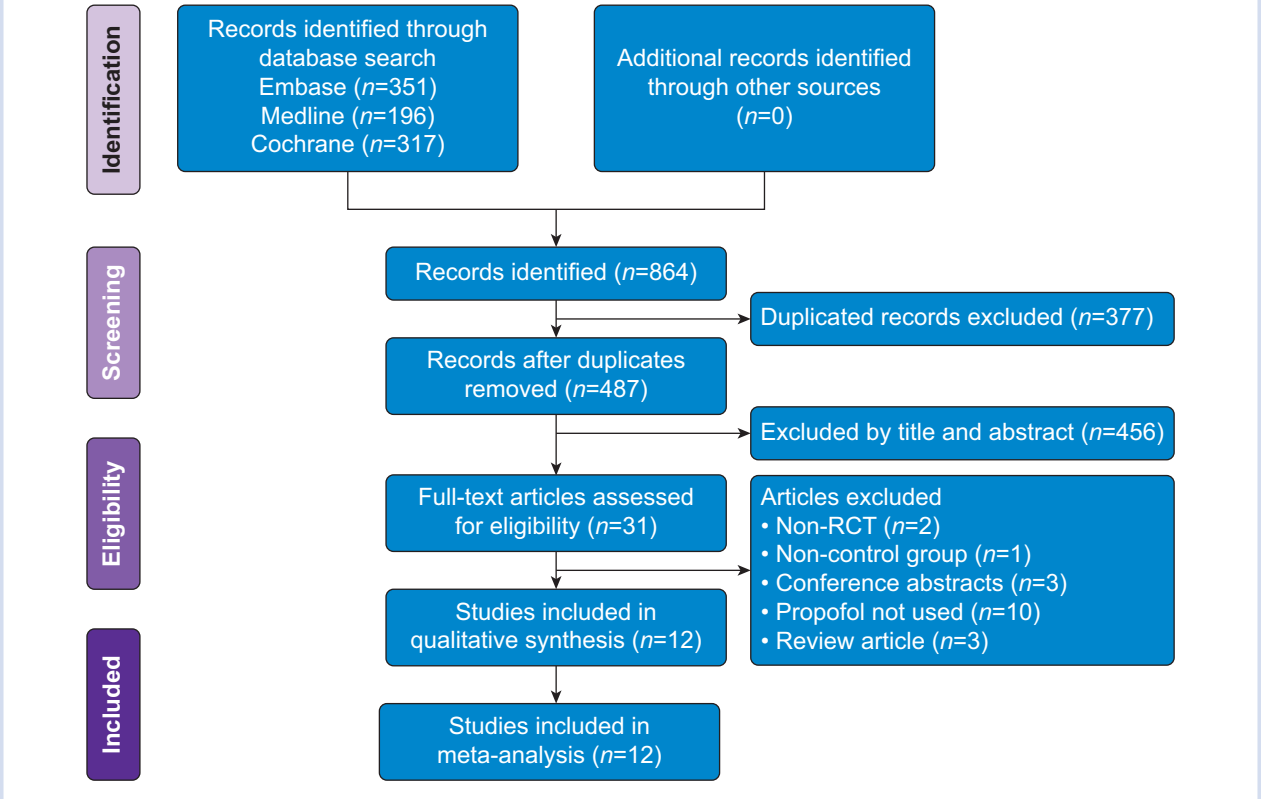

Fig 1. Meta-analysis flowchart for selecting eligible studies.

Table 1 Characteristics of included studies (n=12).

	Age (yr)	Sample size (n)	ASA physical status	Procedure	Lidocaine bolus (mg kg^{-1})	Lidocaine infusion	Sedative adjunct	Country
Ates 2020[25]	62 (20) *vs* 62 (19)	40 *vs* 40	1–3	ERCP	1.5	0	Ketamine	Turkey
Chen 2020[26],†	70.4 (4.5) *vs* 71.4 (5.1)	39 *vs* 40	1–2	Colonoscopy	1.5	4 mg kg^{-1} h^{-1}	Sufentanil	China
de la Morena 2013[27]	49.7 (15.8) *vs* 51.7 (14.9)	59 *vs* 60	1–4	EGD	50 mg lidocaine spray	NA	—	Spain
Forster 2018[21]	56.3 (22.3) *vs* 47.7 (31.8)	21 *vs* 21	1–2	Colonoscopy	1.5	4 mg kg^{-1} h^{-1}	Ketamine	Belgium
Heuss 2011[22]	61 (18) *vs* 61 (18)	147 *vs* 147	1–3	EGD	4 Squirts of 10% lidocaine spray	NA	—	Switzerland
Kim 2016[28]	65.2 (8.5) *vs* 65.0 (9.0)	30 *vs* 31	NA	ESD	1.5	2 mg kg^{-1} h^{-1}	Fentanyl	Korea
Li 2020[29],‡	44.4 (7.1) *vs* 44.9 (7.0)	45 *vs* 45	2–3	Colonoscopy	1.5	2 mg kg^{-1} h^{-1}	—	China
Liu 2021[30]	46.8 (12.7) *vs* 45.0 (10.6)	21 *vs* 27	1–2	Gastroscopy	1.5	0	—	China
Liu 2020[31]	60.6 (13.7) *vs* 62.2 (15.4)	24 *vs* 24	1–3	ERCP	1.5	2 mg kg^{-1} h^{-1}	Midazolam Sufentanil	China
Sun 2018[32]	21–56 *vs* 20–60¶	313 *vs* 313	NA	EGD	60 mg lidocaine spray	NA	—	China
Ullman 2019[34]	55.0 (14.2) *vs* 52.7 (16.0)	46 *vs* 47	1–3	EGD	Gargle 7.5 ml of 2% lidocaine viscous solution	NA	—	USA
Tsai 2012[33]	47.8 (9.7) *vs* 51.0 (9.8)	64 *vs* 65	1–2	Gastroscopy	30 mg lidocaine spray	NA	Fentanyl	Taiwan

EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; NA, not available.
† Focusing on older patients aged ≥65 yr.
‡ Focusing on patients with obesity (BMI ≥30 kg m^{-2}).
¶ Reported as range.

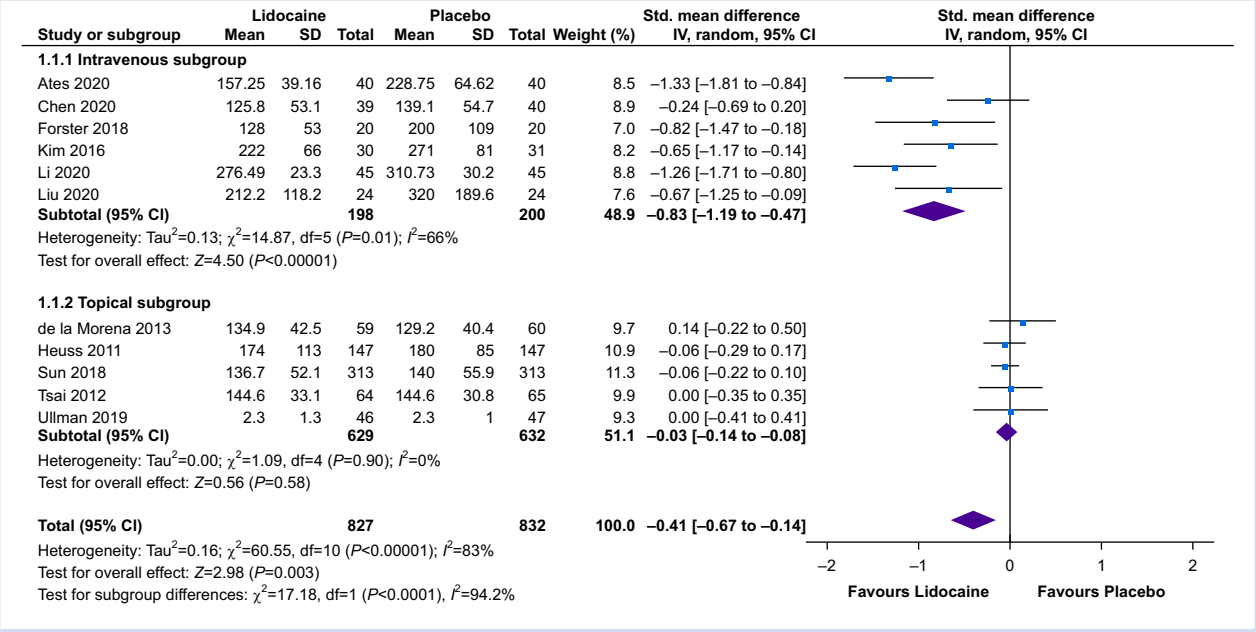

Fig 2. Forest plot for comparing propofol dosage during gastrointestinal endoscopic procedures between lidocaine and placebo groups. CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation; Std, standardised.

whether they were RCTs, for which a further 456 reports were excluded. Of the 31 records eligible for full-text appraisal, 19 were excluded because of inappropriate PICO questions (n=14), not RCTs (n=2), or being conference abstracts (n=3). Finally, a total of 12 RCTs with 1707 patients were included in the present qualitative systematic review.[21,22,25–34]

Study characteristics

Table 1 presents the characteristics of the 12 included studies with 1707 patients published from 2011 to 2020. All studies were conducted in adult patients. Among these studies, one trial investigated patients aged ≥65 yr,[26] while another focused on patients with obesity (i.e. BMI≥30 kg m^{-2}).[29] The goal of sedation for GEPs and sedative techniques are shown in Supplementary Table S2. The sample size of the included trials ranged from 42 to 626. Although four studies included relatively healthy patients (i.e. ASA status of 1–2),[21,26,29,33] six studies also included higher-risk patients (i.e. ASA 3).[22,25,27,29,31,34] However, two trials did not specify the status of patients.[28,32] Seven trials assessed the impact of i.v. lidocaine on clinical outcomes,[21,25,26,28–31] whereas five trials investigated the benefit of topical lidocaine.[22,27,32–34] Focusing on the administration strategy of i.v. lidocaine, two studies[25,30] used an i.v. bolus of 1.5 mg kg^{-1} without subsequent infusion, while the same bolus dosage was adopted followed by a continuous lidocaine infusion at a dose of 4 mg kg^{-1} h^{-1} in two trials[21,26] and 2 mg kg^{-1} h^{-1} in three trials.[28,29,31] Airway manipulation was not required in patients recruited in 10 studies,[21,25–32,34] while two trials reported the need for mask ventilation[22] or airway manipulation (e.g. chin lift or jaw manipulation)[33] in their patients because of oxygen desaturation that subsequently resolved without recourse to advanced airways.

Risk of bias evaluation

The risks of bias of each included study and the overall risk of bias of all studies are summarised in Supplementary Figures S1 and S2, respectively. Details on bias assessment for each trial are shown in Supplementary Table S3. Although all studies described their method of randomisation, information regarding allocation concealment was not provided in six trials.[25,28,30–32,34] The risks of detection bias of all trials were deemed low because all studies tried to blind study participants and personnel from their knowledge of intervention. The risk of attrition bias was also considered to be low as missing outcome data were comparable between the two groups. Besides, since all outcomes of interest for the present study have been reported and all studies were registered in clinical trials, the reporting bias was low. However, the risk of other bias was uncertain in one trial as conflict of interest was not mentioned,[27] while it was high in another trial as some of its authors reported sponsorship from related companies.[21]

Primary outcome and secondary outcomes

Impact of lidocaine on propofol dosage requirement

Eleven studies involving a total of 1659 patients (lidocaine group, n=827 *vs* placebo group, n=832) were available for the analysis.[21,22,25–29,31–34] One trial assessed the median effective dose of propofol for sedation after the addition of i.v. lidocaine during gastroscopy in adult patients.[30] The total dosage of propofol was unavailable in that study.[30] Pooled results demonstrated a lower propofol dosage during GEPs in the lidocaine group compared with that in the placebo group (SMD=−0.41, 95% CI: −0.67 to −0.14, P=0.003; I^2=83%) (Fig. 2). Subgroup analysis showed a significant difference between the i.v. and topical subgroups (P<0.0001). Only i.v. lidocaine

Table 2 Impacts of potential confounding factors on propofol dosage requirement.

	Number of studies	Lidocaine (*n*)	Placebo (*n*)	SMD [95% CI]	*P*-value between subgroups	I^2 between subgroups (%)
Intravenous lidocaine for upper or lower GEPs						
Without adjunct	1	45	45	−1.26 [−1.71 to −0.80]	0.09	66.3
With adjunct	5	153	155	−0.74 [−1.12 to −0.35]		
I.V. lidocaine bolus without infusion	1	40	40	−1.33 [−1.81 to −0.84]	0.05	72.9
I.V. lidocaine bolus with infusion	5	158	160	−0.73 [−1.10 to −0.36]		
Intravenous lidocaine for upper GEPs						
Without adjunct	0	0	0	NA	NA	NA
With adjunct	3	94	95	−0.90 [−1.35 to −0.45]		
Intravenous lidocaine for lower GEPs						
Without adjunct	1	45	45	−1.26 [−1.71 to −0.80]	0.03	77.5
With adjunct	2	59	60	−0.48 [−1.04 to 0.08]		
Topical lidocaine for upper GEPs						
Without adjunct	4	565	567	−0.03 [−0.15 to 0.08]	0.85	0
With adjunct	1	64	65	0.00 [−0.35 to 0.35]		

CI, confidence interval; GEP, gastrointestinal endoscopic procedure; NA, not available; SMD, standardised mean difference.

reduced propofol dosage required for GEPs (SMD=−0.83, 95% CI: −1.19 to −0.47, $P<0.00001$; $I^2=66\%$), while the application of topical lidocaine did not decrease the propofol dosage compared with placebo (SMD=−0.03, 95% CI: −0.14 to 0.08, $P=0.58$; $I^2=0\%$). Sensitivity analysis did not show a significant impact on outcome by omitting certain trials. A funnel plot is shown in Supplementary Figure S3, indicating the presence of publication bias for this outcome.

The impacts of other confounding factors on propofol dosage requirement assessed with subgroup analyses are shown in Table 2. The results showed that the beneficial effect of i.v. lidocaine compared with that of placebo was not

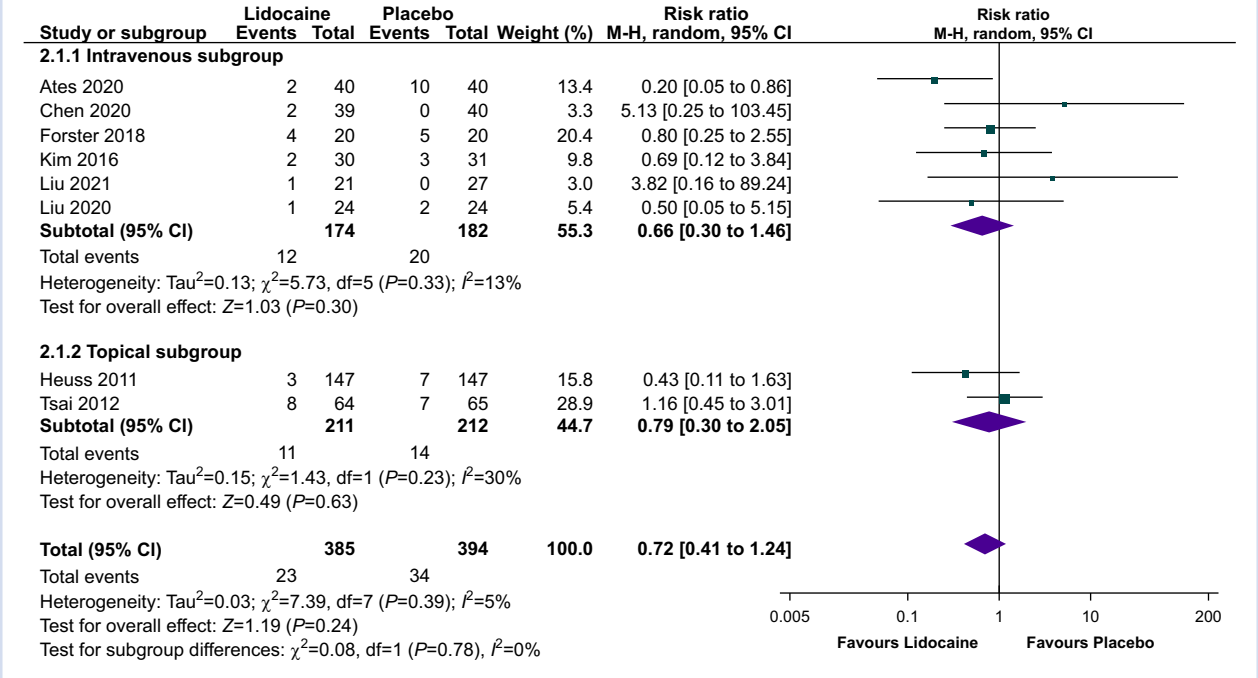

Fig 3. Forest plot for the comparison of risk of oxygen desaturation between lidocaine and placebo groups during gastrointestinal endoscopic procedures. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

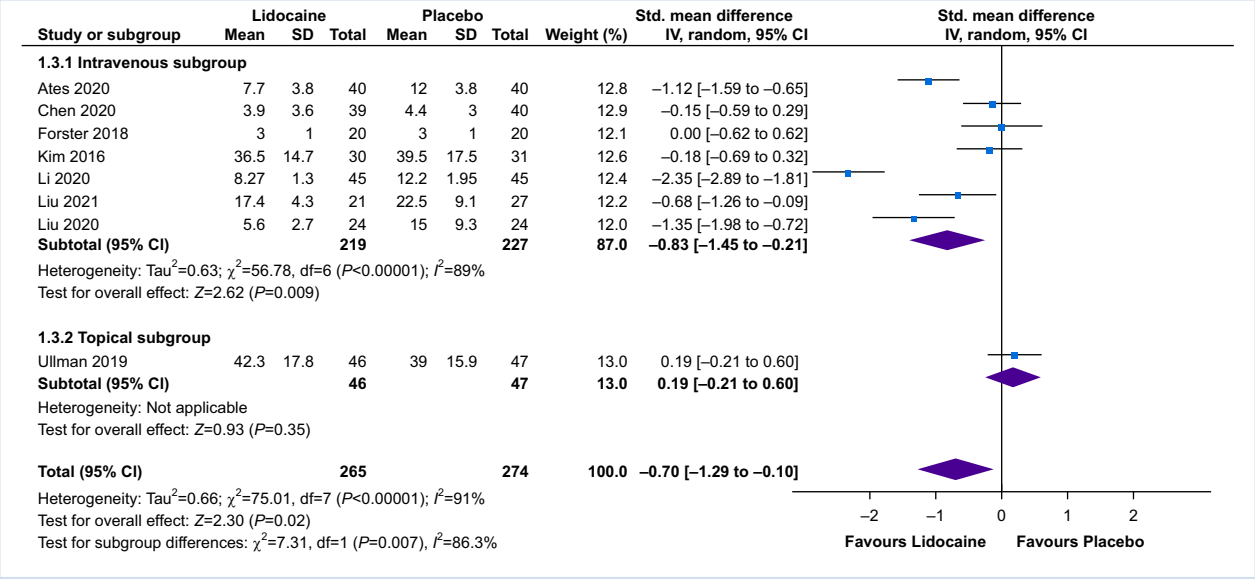

Fig 4. Forest plot for the comparison of recovery time between lidocaine and placebo groups during gastrointestinal endoscopic procedures. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std, standardised.

affected by the addition of anaesthetic adjunct to infused lidocaine (P=0.09). Likewise, the benefit of i.v. lidocaine bolus compared to that of placebo was not affected by the administration of lidocaine infusion in those receiving i.v. lidocaine (P=0.05). However, the beneficial impact of i.v. lidocaine compared with that of placebo in patients undergoing lower GEPs became significantly masked (P=0.03) by the addition of anaesthetic adjuncts into the regimen so that the therapeutic outcomes were comparable between i.v. lidocaine and placebo in this patient subgroup. Moreover, the use of adjunct had no significant impact on the therapeutic outcome between patients receiving upper GEPs with topical lidocaine and those with placebos (P=0.85).

Impact of lidocaine on risk of oxygen desaturation

Eight studies involving a total of 779 patients (lidocaine group, n=385 *vs* placebo group, n=394) reported the incidence of oxygen desaturation for analysis.[21,22,25,26,28,30,31,33] The definitions of oxygen desaturation of the included studies are demonstrated in Supplementary Table S4. The pooled RR of oxygen desaturation was 0.72 (95% CI: 0.41–1.24, P=0.39, I^2=5%) (Fig. 3). The finding showed no significant association between the use of lidocaine and the risk of oxygen desaturation during GEPs. Comparison between the i.v. and topical subgroups also demonstrated no significant difference on subgroup analysis (P=0.78). Sensitivity analysis did not show a significant impact on outcome by omitting certain trials.

Impact of lidocaine application on procedure time

Ten studies with a total of 787 patients (lidocaine group, n=388 *vs* placebo group, n=399) were available for the analysis.[21,25–31,33,34] Inspection of the forest plot revealed no significant difference in procedure time between both groups (SMD=0.13, 95% CI: −0.07 to 0.33, P=0.21; I^2=47%) (Supplementary Fig. S4). No significant difference between i.v. and topical subgroups was noted on subgroup analysis (P=0.33). In addition, sensitivity analysis did not show a significant impact on outcome by omitting certain trials. A funnel plot is shown in Supplementary Figure S5, suggesting the presence of publication bias for this outcome.

Impact of lidocaine application on recovery time

Eight studies recruiting a total of 539 patients (lidocaine group, n=265 *vs* placebo group, n=274) were eligible for the analysis.[21,25,26,28–31,34] A forest plot demonstrated a shorter recovery time after GEPs in the lidocaine group compared with that in the placebo group (SMD=−0.7, 95% CI: −1.29 to −0.1, P=0.02; I^2=91%) (Fig. 4). Subgroup analysis showed a significant difference between the i.v. and topical subgroups (P=0.007). Whereas i.v. lidocaine was associated with a significant reduction in recovery time (SMD=−0.83, 95% CI: −1.45 to −0.21, P=0.009), there was no difference in recovery time between the topical lidocaine and placebo groups (SMD=0.19, 95% CI: −0.21 to 0.60, P=0.35). Omitting two of the trials[25,31] significantly impacted the outcomes on sensitivity analysis. Omitting the study that used ketamine as anaesthesia adjunct to propofol sedation[25] obliterated the overall beneficial effect of i.v. lidocaine on recovery time (SMD=−0.64, 95% CI: −1.31 to 0.03, P=0.06, I^2=91%). Similarly, omitting another study[31] utilising midazolam and sufentanil as anaesthesia adjuncts also rendered the overall benefit of lidocaine on recovery time insignificant (SMD=−0.61, 95% CI: −1.25 to 0.03, P=0.06, I^2=91%).

Impact of lidocaine application on pain or discomfort score

Six studies involving a total of 948 patients (lidocaine group, n=473 *vs* placebo group, n=475) were available for analysis.[21,25,28,31,32,34] The forest plot demonstrated a lower pain or discomfort score among patients receiving lidocaine

than that in those being given placebos (SMD=−0.47, 95% CI: −0.8 to −0.14, P=0.005; I^2=73%) (Supplementary Fig. S6). No significant difference between i.v. and topical subgroups was noted on subgroup analysis (P=0.08). Besides, sensitivity analysis showed no evidence of a significant impact on outcome by omitting certain trials.

Impact of lidocaine application on endoscopist satisfaction

Five studies with 565 patients in total (lidocaine group, n=282 *vs* placebo group, n=283) contained data for the analysis of endoscopist satisfaction.[21,22,29,31,34] A forest plot revealed a higher endoscopist satisfaction in the lidocaine group than that in the placebo group (SMD=0.48, 95% CI: 0.06–0.9, P=0.03; I^2=79%) (Supplementary Fig. S7). Subgroup analysis showed a significant difference between the i.v. and topical subgroups (P=0.03). Only the application of i.v. lidocaine increased the endoscopist satisfaction compared with placebo (SMD=0.75, 95% CI: 0.21–1.29, P=0.006; I^2=65). The endoscopist satisfaction became insignificant by omitting two of the trials on sensitivity analysis, including a study using ketamine as anaesthesia adjunct to propofol sedation[21] and another trial incorporating midazolam and sufentanil into the propofol sedation regimen.[31]

Impact of lidocaine application on patient satisfaction

The forest plot on patient satisfaction demonstrated no significant difference between the two groups (SMD=0.64, 95% CI: −0.04 to 1.33, P=0.06; I^2=89%) (Supplementary Fig. S8).[29,31,32] Moreover, no significant difference between i.v. and topical subgroups was found on subgroup analysis (P=0.22). On sensitivity analysis, omitting one trial[29] that did not use any anaesthesia adjunct to propofol sedation rendered the patient's satisfaction significant (SMD=0.27, 95% CI: 0.12–0.42, P=0.0004; I^2 = 0%).

Impact of lidocaine application on risk of adverse events

The effects of lidocaine use on the risks of hypotension, vomiting/nausea, procedure-associated gag events, and involuntary movement are shown in Supplementary Figures S9–S12, respectively. Overall, lidocaine treatment decreased the risk of gag event (RR=0.51, 95% CI: 0.35–0.75, P=0.0006, I^2=0%) (Supplementary Fig. S11)[22,25,28,33] and involuntary movement (RR=0.4, 95% CI: 0.16–0.96, P=0.04, I^2=34%) (Supplementary Fig. S12),[28,31,33] but not the risk of hypotension (RR=0.6, 95% CI: 0.22–1.65, P=0.32, I^2=21%) (Supplementary Fig. S9)[25,29–31] or vomiting (RR=0.75, 95% CI: 0.42–1.34, P=0.32, I^2=0%) (Supplementary Fig. S10).[25,28,29,31] For gag events, hypotension, and vomiting, sensitivity analysis showed no significant influence on outcome by omitting certain trials. However, for involuntary movement, omitting two trials one at a time on sensitivity analysis rendered the overall difference insignificant. Of the two trials, one applied fentanyl[28] and the other used midazolam and sufentanil[31] as anaesthesia adjuncts to propofol sedation, respectively.

Discussion

Our results demonstrated that the addition of i.v. or topical lidocaine to the propofol sedation regimen during GEPs could decrease the level of post-procedural pain, risk of gag events, and involuntary movement without significant impacts on haemodynamic and respiratory profiles. Nevertheless, subgroup analysis showed that only i.v. lidocaine was able to reduce propofol dosage required for GEPs, increase endoscopist satisfaction, and shorten recovery time without adversely affecting the smoothness of procedures for the endoscopists (i.e. procedure time).

Since GEPs are commonly performed in older patients with multiple comorbidities,[25,26,35] the increase in susceptibility to serious adverse reactions (e.g. hypoventilation and apnoea) as a result of age-related changes in pharmacokinetics and pharmacodynamics is another concern.[36] Besides, the narrow window between light and deep propofol sedation with respiratory suppression and the danger of severe apnoea remain critical issues.[37] As propofol-associated adverse events are often dose-dependent,[38] the propofol-sparing effect of i.v. lidocaine may reduce the risk of cardiopulmonary complications, especially in the older population. However, the current study showed that the reduction in propofol dosage associated with i.v. lidocaine was unable to decrease the risk of hypoxemia or hypotension compared with that with placebo. Therefore, our findings highlighted the importance of careful monitoring and implementation of appropriate preventive strategies (e.g. oxygen supplementation) by healthcare providers who can assess the patients' airway, ventilation efficacy, and haemodynamic state, even at a reduced propofol dosage when i.v. lidocaine is used as an anaesthetic adjunct to enable immediate response on encountering respiratory or haemodynamic compromise in patients undergoing sedation for GEPs.

Notwithstanding the reported effectiveness of topical pharyngeal lidocaine spray for alleviating discomfort and improving the ease of GEPs in conscious patients without sedation,[39] the impact of topical anaesthesia on GEPs in sedated patients remains controversial. Some studies demonstrated that topical anaesthesia with lidocaine spray facilitates upper GEPs for endoscopists and improves patient tolerance in those receiving conscious sedation with diazepam,[40] despite the failure to reproduce the results by other authors in a similar setting (i.e. conscious sedation).[41,42] Although a previous meta-analysis[43] showed that a combination of pharyngeal anaesthesia and sedation was associated with a good tolerance to gastroscopy from a patient's perspective and an easier procedure for the endoscopist, the included RCTs had notable heterogeneity and i.v. propofol was not used. In contrast, our meta-analysis demonstrated that topical lidocaine was unable to reduce the propofol dosage required for GEPs. However, we found that the application of topical lidocaine could reduce the risk of gag events and improve procedure-associated pain or discomfort score. Therefore, topical lidocaine may still be recommended for patients undergoing GEPs under propofol sedation.

In the current meta-analysis, neither i.v. nor topical lidocaine could reduce the procedure time required for GEPs. Notwithstanding the lack of a notable impact on the procedure time, i.v. lidocaine was associated with a significant reduction in the recovery time compared with that in the placebo group (Fig. 4). Our finding was consistent with that of previous studies suggesting that the use of i.v. lidocaine may improve postoperative recovery such as recuperation of gastrointestinal function, a decreased incidence of postoperative nausea and vomiting, and shortening of hospital stay.[44–47] As the majority of GEPs are performed in an outpatient setting, the use of i.v. lidocaine may enhance endoscopy unit efficiency by shortening the recovery time.

In the current meta-analysis, we found an increased endoscopist satisfaction with GEPs in patients receiving i.v. lidocaine. However, there was no difference in patient satisfaction between the lidocaine (i.e. i.v. or topical) and placebo groups. Since previous studies have reported an association of patient satisfaction with the degree of discomfort and pain regarding the procedures,[48,49] the finding of a lower pain/discomfort score associated with the use of i.v. or topical lidocaine without a corresponding increase in patient satisfaction compared with that with placebos in the current study appears inconsistent. There may be several possible explanations. First, the on-site acquisition of patients' responses may suppress their free expression of dissatisfaction when confronted with clinical staff, even in those in the placebo group.[50] This was supported by the previous finding that demonstrated a higher degree of satisfaction in on-site surveys than that in mail-back surveys.[51] Second, data from patients shortly after sedation may not accurately reflect their true responses,[50] leading to a potential bias.

Regarding the potential variable patient responses because of their specific body conditions, a previous study on obese individuals undergoing advanced endoscopic procedures revealed a highly significant positive association between an increasing BMI and the degree of hypoxemia during the procedures.[52] Another study demonstrated a lower dose of propofol required for GEPs in older patients compared with that in the younger population.[53] Besides, one[28] of our included studies recruiting patients with gastric neoplasms demonstrated high proportions of comorbidities such as a history of snoring (i.e. 63%) in the lidocaine group. Since snoring is suggestive of an increased upper airway resistance and pharyngeal collapsibility associated with the development of obstructive sleep apnoea (OSA),[54] a higher risk of cardiopulmonary adverse events (e.g. hypoxia) in those with OSA receiving colonoscopy independent of BMI and sedation type[55] may contribute to bias in our study outcomes.

An investigation into the effects of some potential confounders (i.e. use of anaesthetic adjuncts, lidocaine infusion, nature of procedures) on propofol dosage requirement in the current study demonstrated no significant impact of either the use of anaesthetic adjunct or lidocaine infusion on the beneficial influence of i.v. lidocaine on reducing propofol requirement compared with that of placebo when the nature of the procedures was not considered. However, the benefit was masked in patients undergoing lower GEPs when anaesthetic adjuncts were used. The finding may be attributed to a lower degree of irritation associated with lower GEPs compared with those performed in the upper gastrointestinal tract.

The current meta-analysis had its limitations. First, apart from the potential publication bias from under-reporting identified in the current meta-analysis, the wide variation in recovery time may be attributed to the heterogeneity arising from differences in the GEPs performed, the infusion dosage of propofol, the goals of sedation, and the patient population included (e.g. older or obese patients), and the use of sedative adjuncts (e.g. ketamine). Second, the possibility of bias from oversedation cannot be ruled out because of a lack of objective criteria for the assessment of sedative level in all included studies. Third, the use of anaesthetic adjuncts and the procedures chosen (e.g. upper *vs* lower GEPs) may affect the benefit of i.v. lidocaine compared with that of placebo and contribute to bias. Moreover, the small number of available trials and the high heterogeneity between the subgroups may blemish the reliability of the results of our subgroup analyses. Therefore, further large-scale RCTs are warranted to verify our findings before their clinical application.

In conclusion, the use of i.v. or topical lidocaine as anaesthesia adjuncts for patients under propofol sedation during gastrointestinal endoscopic procedures decreased the level of post-procedural pain and the risks of gag events and involuntary movement without affecting the haemodynamic and respiratory profiles. Furthermore, i.v. lidocaine could reduce propofol dosage, increase endoscopist satisfaction, and shorten recovery time without compromising the ease of procedure for endoscopists (i.e. procedure time). There were no differences in patient satisfaction and risk of vomiting/nausea between patients with i.v. or topical lidocaine and those without. Because of potential publication bias and the inconsistent outcomes of sensitivity analysis among the included trials, further studies are required to support our findings.

Author contributions

Conceptualisation and literature search: K-CH, MY
Methodology: Y-TL
Trial selection: J-YC, L-KW
Data analysis: Y-JC, Y-PC
Data extraction: K-ML, C-NH
Writing—original draft preparation: K-CH, MY
Writing—review and editing: K-CH, C-KS
Read and agreed to the published version of the manuscript: all authors.

Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.08.036.

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