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Prevention of pain on injection of propofol: systematic review and meta-analysis

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ABSTRACT

Objective To systematically determine the most efficacious approach for preventing pain on injection of propofol.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Cochrane Library, www.clinicaltrials.gov, and hand searching from the reference lists of identified papers.

Study selection Randomised controlled trials comparing drug and non-drug interventions with placebo or another intervention to alleviate pain on injection of propofol in adults.

Results Data were analysed from 177 randomised controlled trials totalling 25 260 adults. The overall risk of pain from propofol injection alone was about 60%. Using an antecubital vein instead of a hand vein was the most effective single intervention (relative risk 0.14, 95% confidence interval 0.07 to 0.30). Pretreatment using lidocaine (lignocaine) in conjunction with venous occlusion was similarly effective (0.29, 0.22 to 0.38). Other effective interventions were a lidocaine-propofol admixture (0.40, 0.33 to 0.48); pretreatment with lidocaine (0.47, 0.40 to 0.56), opioids (0.49, 0.41 to 0.59), ketamine (0.52, 0.46 to 0.57), or non-steroidal anti-inflammatory drugs (0.67, 0.49 to 0.91); and propofol emulsions containing medium and long chain triglycerides (0.75, 0.67 to 0.84). Statistical testing of indirect comparisons showed that use of the antecubital vein and pretreatment using lidocaine along with venous occlusion to be more efficacious than the other interventions.

Conclusions The two most efficacious interventions to reduce pain on injection of propofol were use of the antecubital vein, or pretreatment using lidocaine in conjunction with venous occlusion when the hand vein was chosen. Under the assumption of independent efficacy a third practical alternative could be pretreatment of the hand vein with lidocaine or ketamine and use of a propofol emulsion containing medium and long chain triglycerides. Although not the most effective intervention on its own, a small dose of opioids before induction halved the risk of pain from the injection and thus can generally be recommended unless contraindicated.

INTRODUCTION

Propofol is the drug of choice for induction of anaesthesia in millions of patients every year because of its rapid onset and short duration of action, easy titration, and favourable profile for side effects.[1] Despite these positive attributes, about three out of five patients experience pain on injection of propofol, with one of these patients reporting severe or excruciating pain. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period. As a result several interventions have been investigated to alleviate the pain associated with propofol injection. A systematic review in 2000 suggested pretreatment using lidocaine (lignocaine) in conjunction with venous occlusion as the most effective intervention.[2] Despite that recommendation the technique failed to gain widespread popularity, possibly because of the time needed to apply the tourniquet. As a result the pain associated with injection of propofol remains a challenge and more than 100 new studies have explored additional and alternative strategies. These include novel propofol emulsions,[3 4] modified emulsions, and microemulsion formulations,[5-7] as well as diverse drugs and their combinations. We summarised all the available evidence from trials that compared the use of any drug or non-drug interventions (or combinations) with an active or inactive control in adults receiving intravenous propofol.

METHODS

The study was carried out according to the methods recommended by the Cochrane Collaboration and written in accordance with the PRISMA statement for reporting systematic reviews.[8 9]

This qualitative systematic review included studies published up to December 2010. We searched PubMed, Cochrane Library, and Embase using the search terms "propofol" AND ("injection pain" OR "pain on injection"). We limited our search to clinical trials and randomised controlled trials (see web extra 1 for details of search strategy).

To identify all available evidence we identified additional relevant randomised controlled trials by hand

Table 1 | Summary of most effective interventions for reducing pain from propofol injection

Interventions	No of patients	No of studies	Control intervention*	Relative risk† (95% CI)
Propofol injection in antecubital vein	411	6	Hand vein	0.14 (0.07 to 0.30)
Lidocaine pretreatment with venous occlusion	1072	14	No venous occlusion	0.29 (0.22 to 0.38)
Lidocaine-propofol admixture	3210	25	No pretreatment	0.40 (0.33 to 0.48)
Lidocaine pretreatment	2053	24	No pretreatment	0.47 (0.40 to 0.56)
Opioid pretreatment	1522	17	No pretreatment	0.49 (0.41 to 0.59)
Ketamine pretreatment	910	7	No pretreatment	0.52 (0.46 to 0.57)
NSAID pretreatment	628	7	No pretreatment	0.67 (0.49 to 0.91)
Propofol emulsion, medium and long chain triglycerides	2344	24	Propofol emulsion, long chain triglycerides	0.75 (0.67 to 0.84)

NSAID=non-steroidal anti-inflammatory drug.
*Control groups all received propofol emulsion containing long chain triglycerides. Propofol was injected in hand vein in all treatment and control groups except group assigned to antecubital vein.
†Mantel Haenszel random effects model.

searching the reference lists of the original papers until no further relevant references could be found. We also searched reviews on pain associated with propofol injection for similar randomised controlled trials. Although we applied no language restrictions, the only relevant studies were in English, German, and Japanese.

To minimise data duplication as a result of multiple reporting we compared papers from the same author. In addition, we searched www.clinicaltrials.gov for studies. Two authors (LJ and VK) screened and retrieved reports and excluded irrelevant studies. Relevant data were extracted by one author (VK) and checked by another (LJ). Additional investigators (CCA, OR, and NLP) participated in the review process when uncertainty about eligibility criteria arose. From each study we extracted details on patients' characteristics (adults only), use of non-drug interventions (for example, site of venous cannulation, speed of injected propofol, temperature of injected propofol), use of analgesic interventions, and use of combinations of interventions (see web extra 2 for characteristics of included studies).

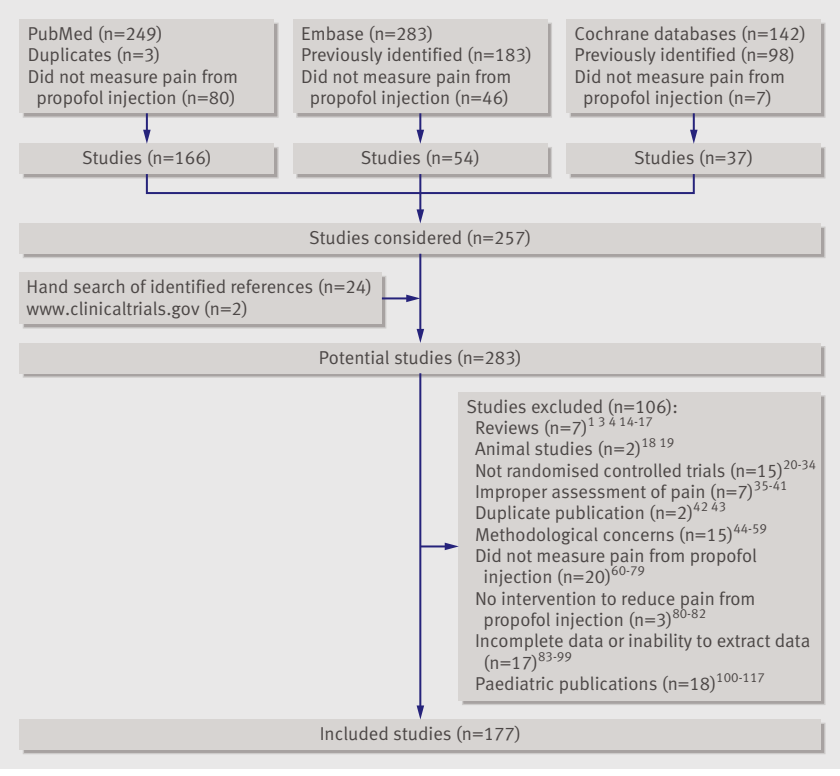

Fig 1 | Flow of papers through study

Selection of studies for review

Selected studies included all randomised controlled trials that compared the use of any drug or non-drug intervention, or a combination, with an active or inactive control, and reported the response rate and severity of pain in adults receiving intravenous propofol. All included studies had numerical data presented in the text or a table; if data were not presented as such, we extracted the information from the graphs if the scale allowed a sufficiently precise estimation. We included all studies that met the eligibility criteria, regardless of language of publication.

Assessment of risk of bias

We assessed risk of bias in each of four domains in studies meeting the inclusion criteria: adequate sequence generation, adequate concealment of allocation, adequate blinding, and completeness of reporting data on outcomes (see web extra 2). The specific domains of risk of bias were graded as "yes" for low risk, "unclear," and "no" for high risk. As more than 95% of the primary studies were designed to search for pain reduction during anaesthesia induction with propofol, selective outcome reporting bias was considered unlikely and not assessed.

Statistical analysis

Meta-analyses were carried out by direct comparisons of intervention versus control (pairwise) and indirect comparisons between the network of interventions shown to be significant individually. The primary outcome was the number of patients reporting any pain

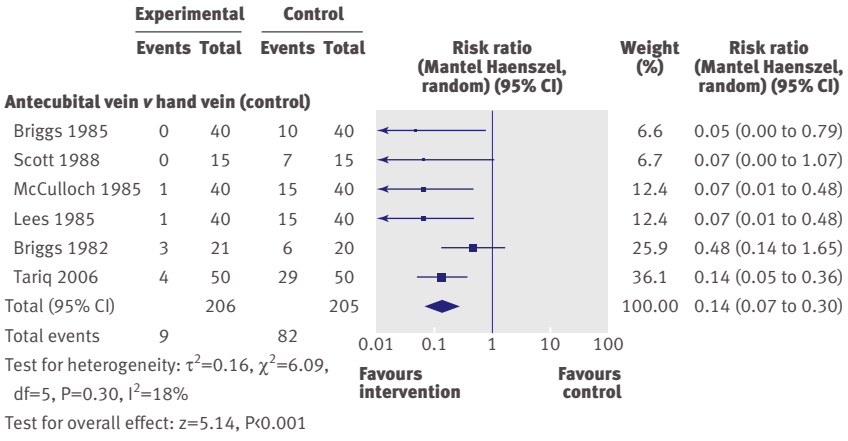

Fig 2 | Risk of pain on injection of propofol in antecubital vein or hand vein

(pain response rate); the effect size was the relative risk. We did not carry out meta-analyses of pain scores (for example, numerical or verbal rating scales) because they were reported both rarely and inconsistently. For studies with multiple intervention groups, we partitioned the count of events and patients in the control group into two or more control groups within any meta-analysis to avoid a unit of analysis error. Similarly, for the studies participating in the indirect comparisons, we partitioned the comparator group according to how many times it was used for indirect comparisons (across meta-analyses). The summary relative risks and 95% confidence intervals were estimated using a random effects Mantel-Haenszel method in RevMan 5.0 (Cochrane Collaboration). Statistical heterogeneity was assessed by the I^2 value. If interventions involved 10 or more studies, we used funnel plots to visualise small study effects or reporting bias; asymmetry was tested using the arcsine transformation and method of moments linear regression implemented in the R package meta (R Foundation for Statistical Computing, Austria).[10] We considered P values less than 0.05 and relative risks not crossing the identity line as statistically significant.

We analysed the network of randomised controlled trials within an indirect comparison framework using previously described models[11] and implemented in frequentist mixed effects metaregression[12]; we selected only interventions that significantly reduced pain by a direct intervention comparison with six or more included studies. The summary statistic was the relative risk, with 95% confidence intervals. The common comparator was the placebo or control group. The moderators in the mixed effects models were the interventions entered as categorical covariates. Assumptions in this analysis included a sufficient homogeneity of the different trials, treatment effects (logRR) distributed normally around a typical value, and the same residual heterogeneity (τ^2) among the moderators. This analysis was carried out using the R package metafor using restricted maximum likelihood estimation (see web extra 3 for details of the model). We adjusted the test statistics of individual estimates of moderator variables and omnibus hypotheses of all moderators by the method of Knapp and Hartung (t and F distributions).[13] Residual heterogeneity was assessed by χ^2 tests. As the methods of estimation are different, the relative risk values from RevMan and metafor differ slightly.

RESULTS

A search of PubMed, Embase, and Cochrane databases identified 674 potentially relevant papers (fig 1), of which 427 were excluded: 83 of the 249

Table 2 | Efficacy results of non-drug interventions to alleviate the pain from propofol injection

Intervention	Control	No of studies	No of patients	Relative risk* (95% CI)	Heterogeneity I^2 (%), P value	References
Bacteriostatic saline	None	1	78	0.45 (0.30 to 0.69)	NA	138
Speed of intravenous carrier fluid	No intravenous carrier fluid	4	299	1.16 (0.98 to 1.36)	0, 0.50	119;122;245;246
Microfiltration	No filter	2	455	0.82 (0.51 to 1.34)	92, <0.001	127;128
Mechanical interventions	No intervention	4	291	0.69 (0.38 to 1.25)	0.86, <0.001	30;121;122;174;247
Rate of propofol infusion:						
Overall	—	3	181	0.84 (0.48 to 1.49)	75, 0.02	
Fast infusion	About 2.5 mL/sec	1	30	1.57 (0.84 to 2.92)	NA	119
2 mL/sec	1 mL/sec	1	100	0.48 (0.27 to 0.85)	NA	120
1 mL/sec	13.3 mL/sec	1	51	0.83 (0.62 to 1.12)	NA	248
Temperature of infused propofol:						
4°C	Room temperature	9	583	0.82 (0.64 to 1.04)	81, <0.001	90;129;130;132-137
37°C	Room temperature	4	301	0.91 (0.65 to 1.27)	83, <0.001	131;135-137
Site of injection:						
Overall	—	7	437	0.14 (0.07 to 0.27)	6, 0.38	
Antecubital fossa vein	Hand vein	6	411	0.14 (0.07 to 0.30)	18, 0.30	119;123-126;139
Central vein	Peripheral vein	1	26	0.07 (0.00 to 1.06)	NA	122
Venous occlusion	No venous occlusion	1	22	0.82 (0.35 to 1.89)	NA	119

NA=not applicable.
*Mantel Haenszel random effects model.

Table 3 | Efficacy results of drug interventions to reduce pain from propofol injection

Intervention	Control	No of studies	No of patients	Relative risk* (95% CI)	Heterogeneity I^2 (%), P value	References
α_2 agonist pretreatment	No pretreatment	2	181	0.81 (0.68 to 0.97)	56, 0.13	249;250
Antiemetic pretreatment	No pretreatment	5	430	0.47 (0.32 to 0.69)	61, 0.04	161;162;167;235;251
Barbiturates:						
Pretreatment	No pretreatment	1	108	0.30 (0.14 to 0.62)	38, 0.18	166
Admixture	No admixture	4	363	0.50 (0.28 to 0.89)	85, <0.001	133;252-254
Benzodiazepine pretreatment	No pretreatment	4	270	0.78 (0.34 to 1.77)	81, 0.001	255-258
Cholinesterase inhibitor pretreatment	No pretreatment	1	70	0.53 (0.36 to 0.78)	NA	259
Dextrose 5% in Ringer's lactate solution-propofol admixture	No admixture	1	56	0.48 (0.27 to 0.85)	NA	156
Kallikrein inhibitor pretreatment	No pretreatment	2	413	0.61 (0.52 to 0.72)	0, 0.78	135;260
Lidocaine:						
Admixture	No admixture	25	3210	0.40 (0.33 to 0.48)	79, <0.001	
5-10 mg lidocaine	No admixture	9	963	0.44 (0.32 to 0.60)	78, <0.001	125;126;140;141;143;144;148;150;158
20-30 mg lidocaine	No admixture	7	490	0.37 (0.24 to 0.56)	76, <0.001	138;140;142;144;146;148;158
>40 mg lidocaine	No admixture	18	1757	0.38 (0.29 to 0.50)	81, <0.001	135;140;141;144-147;149;151-153; 156-160;181;261
Admixture	Lidocaine+propofol					
Barbiturate-propofol admixture	Lidocaine+propofol	2	196	0.54 (0.26 to 1.11)	52, 0.12	262;263
Pretreatment	No pretreatment	24	2053	0.47 (0.40 to 0.56)	61, <0.001	
5-20 mg lidocaine	No pretreatment	13	1104	0.54 (0.45 to 0.65)	36, 0.07	119;125;146;150;165;167;170;171; 173-176;200
30-40 mg lidocaine	No pretreatment	7	464	0.38 (0.25 to 0.58)	68, <0.01	159;165;166;168;169;171;177
>50 mg lidocaine	No pretreatment	6	485	0.40 (0.22 to 0.70)	81, <0.001	70;150;161-164
Pretreatment:	Admixture	12	1547			
Ketamine pretreatment	Lidocaine+propofol	1	89	0.10 (0.04 to 0.23)	NA	264
Antiemetic pretreatment	Lidocaine+propofol	1	100	0.44 (0.19 to 1.00)	NA	265
Kallikrein inhibitor pretreatment	Lidocaine+propofol	1	303	0.97 (0.61 to 1.53)	NA	266
Stimulant pretreatment	Lidocaine+propofol	1	156	0.54 (0.40 to 0.74)	0, 0.80	267
Magnesium sulphate pretreatment	No pretreatment	3	400	0.41 (0.34 to 0.51)	0, 0.92	168;268;269
Nitroglycerine pretreatment	No pretreatment	3	269	0.55 (0.32 to 0.97)	88, <0.001	270-272
Nitrous oxide pretreatment:						
Nitrous oxide+oxygen	Oxygen pretreatment	1	90	0.42 (0.24 to 0.75)	NA	273
Nitrous oxide+oxygen pretreatment	Lidocaine+propofol	3	245	0.41 (0.27 to 0.62)	0, 0.43	273-275
Ketamine pretreatment	No pretreatment	7	910	0.56 (0.47 to 0.67)	66, <0.001	164;168;192-196
NSAIDs pretreatment	No pretreatment	7	628	0.67 (0.49 to 0.91)	69, <0.001	147;177;197-201
Opioids pretreatment	No pretreatment	17	1522	0.49 (0.41 to 0.59)	63, <0.001	70;161;163;173;179-191
1% propofol concentration	2% propofol	1	49	2 13 (0.45 to 10.12)	NA	276
Propofol pretreatment	No pretreatment	1	60	0.20 (0.07 to 0.62)	NA	256
1% microemulsion propofol (Aquafol; Daewon Pharmaceutical, Seoul, Republic of Korea)	Long chain trigylcerides	1	288	10.52 (6.06 to 18.27)	NA	86
Propofol emulsions:						
Medium and long chain triglycerides	Long chain triglycerides	24	2344	0.75 (0.67 to 0.84)	57, <0.001	5;6;151;177;197;202-219
Propofol emulsions+lidocaine	Propofol emulsion	12	2240	0.61 (0.44 to 0.84)	83, <0.001	149;151;203;206;220-227
Stimulants pretreatment	No pretreatment	2	208	0.56 (0.34 to 0.93)	84, <0.001	277;278
Steroids pretreatment	No pretreatment	1	70	0.41 (0.24 to 0.69)	NA	279
Topical anaesthetics	Placebo ointment	4	369	0.66 (0.42 to 1.01)	76, <0.01	153;160;176;280
Vasodilator pretreatment	No pretreatment	1	120	0.39 (0.26 to 0.59)	NA	281
Multiple drugs or interventions:		7	533			
Opioid+benzodiazepine pretreatment	Normal saline pretreatment	1	50	0.33 (0.12 to 0.89)	NA	190
Opioid+benzodiazepine+lidocaine pretreatment	Opioid pretreatment	1	46	0.07 (0.01 to 0.49)	NA	282
Opioid+benzodiazepine pretreatment	Opioid pretreatment	1	48	0.31 (0.11 to 0.84)	NA	282
Opioid-lidocaine admixture	Opioid pretreatment	1	48	0.62 (0.28 to 1.36)	NA	282
Opioid pretreatment and lidocaine-propofol admixture	Opioid pretreatment	1	102	0.27 (0.11 to 0.66)	NA	262
Nitrous oxide pretreatment+lidocaine pretreatment	Nitrous oxide pretreatment	1	66	0.36 (0.15 to 0.88)	NA	274
Ketamine pretreatment followed by lidocaine-propofol admixture	Saline pretreatment	1	122	0.22 (0.09 to 0.54)	NA	264
Benzodiazepine (oral)+NSAID (oral)+paracetamol (acetaminophen, oral)+opioid pretreatment (intravenous)	Saline pretreatment	1	209	0.60 (0.42 to 0.85)	NA	283

NA=not applicable; NSAID=non-steroidal anti-inflammatory drug.
*Mantel Haenszel random effects model.

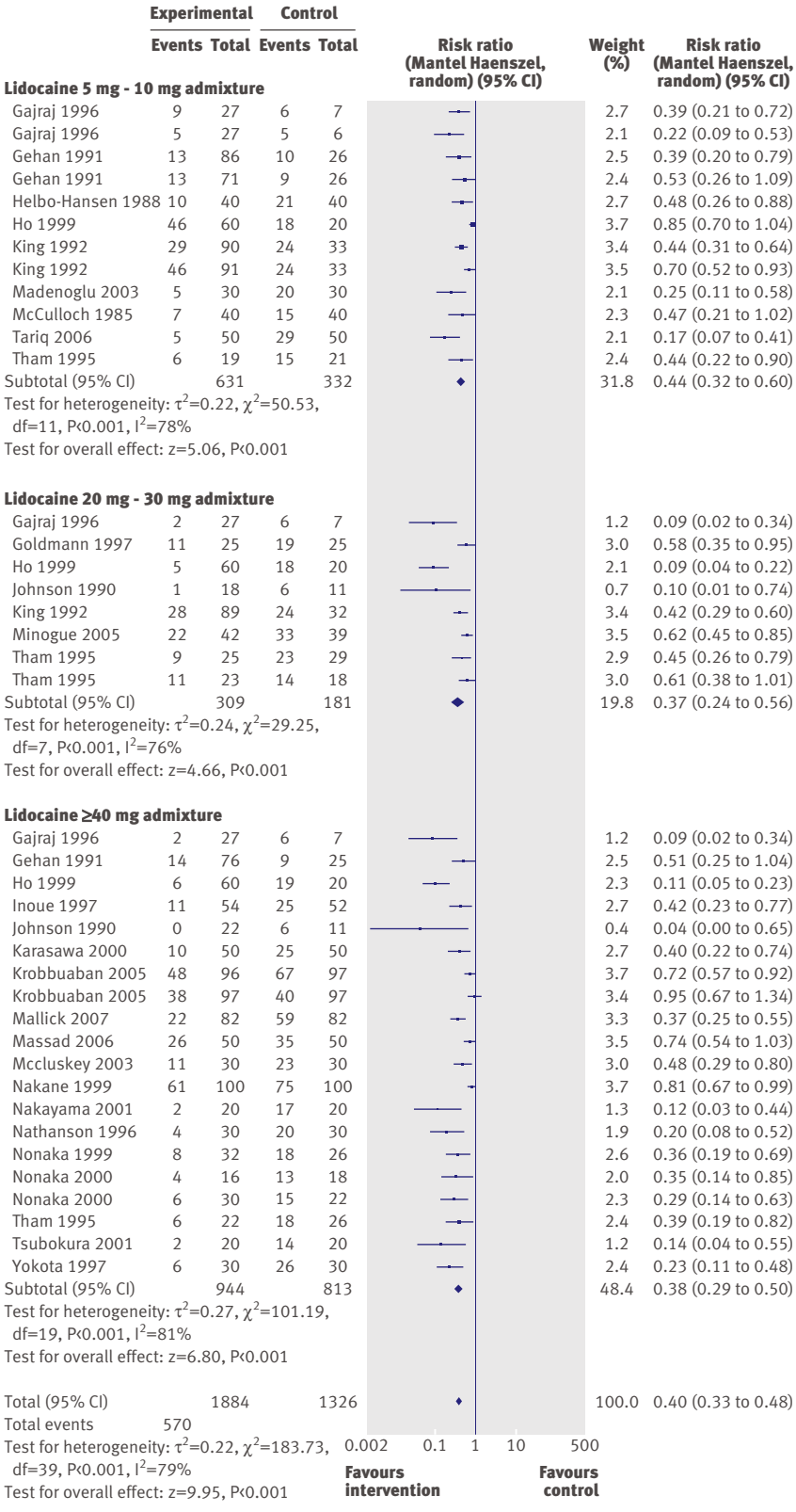

Fig 3 | Risk of pain on injection of lidocaine-propofol admixture

identified through PubMed (three were duplicates and 80 did not measure pain from propofol injection), 229 of the 283 identified through Embase (183 were identified in the previous search and 46 did not measure pain from propofol injection), and 105 of the 142 identified through the Cochrane databases (98 were previously identified and seven did not measure pain from propofol injection). In addition to the 257 potential studies a further 24 were identified after hand searching references of relevant papers, and two were from the US government clinical trials website (www.clinicaltrials.gov). Thus, 283 studies were retrieved as potential clinical trials for further evaluation. A further 106 studies were excluded for the following reasons: reviews (seven studies),[13 14 14-17] not carried out in humans (n=2),[18 19] not randomised controlled trials (n=15),[20-34] improper assessment of pain (n=7),[35-41] duplicate publication (n=2),[42 43] methodological concerns (n=15),[44-59] did not measure pain on injection of propofol (n=20),[60-79] intervention not aimed at pain reduction on injection of propofol (n=3),[80-82] incomplete data or inability to extract data (n=17),[83-99] and studies in children (n=18).[100-117] Thus 177 studies were included in the analysis.

Overall, a low risk of bias was identified for adequate sequence generation in 40% of included studies (n=71), adequate allocation concealment in 43% (n=76), blinding in 85% (n=151), and whether incomplete outcome data were addressed in 88% (n=156).

Thus this systematic review includes data from 25 260 adults (177 randomised controlled trials). The average trial size was 142 patients (range 24 to 388). Nineteen drugs and eight different non-drug interventions and combinations were tested (see web extra figure). About 60% of patients in the control group reported pain on injection of propofol alone. Trials reported pain scores rarely and on different scales. Therefore this analysis is based exclusively on the response rate of pain.

Because of the wide variety of interventions investigated, three categories of studies were established: non-drug interventions, drug interventions and their combinations, and both drug and non-drug interventions. Each category was further divided into several subcategories. Finally, subanalyses were carried out for interventions involving more than five studies.

Efficacy according to categories

Non-drug category

The non-drug category consisted of studies that used mechanical interventions such as different infusion rates,[118-120] venous occlusion,[119] needle sizes,[121] injection sites,[122-126] microfiltration,[127 128] temperature,[90 129-137] and bacteriostatic saline.[138] The most efficacious intervention in this subcategory was selection of an antecubital vein compared with a hand vein as the injection site (relative risk 0.14, 95% confidence interval 0.07 to 0.30; table 1 and fig 2).[119 123-126 139] Conversely, non-effective interventions were cold propofol (4°C), propofol at room temperature, venous occlusion by itself, and modifying the speed of the intravenous carrier fluid (table 2).

Drug category

The drug category comprised various drugs or drug combinations (table 3). The studies were divided into

Table 4 | Efficacy results of drug and non-drug interventions to reduce pain from propofol injection

Intervention	Control	No of studies	No of patients	Relative risk* (95% CI)	Heterogeneity I^2 (%), P value	References
Ionophoretically applied lidocaine	Sham	1	40	0.31 (0.14 to 0.69)	NA	237
Site of injection (antecubital or dorsum):						
Lidocaine (antecubital)	Propofol (antecubital)	2	105	0.18 (0.04 to 0.86)	27, 0.24	119;126
Lidocaine+propofol (antecubital)	Lidocaine+propofol (dorsum)	1	75	0.80 (0.17 to 3.84)	0, 0.07	126
Pethidine+atropine pretreatment and propofol (antecubital)	Pethidine+atropine pretreatment and propofol (dorsum)	2	130	0.17 (0.05 to 0.55)	0, 0.81	123;124
Diazepam (oral) pretreatment and propofol (antecubital)	Diazepam (oral) pretreatment and propofol (dorsum)	2	113	0.10 (0.01 to 0.79)	0, 0.03	123;124
Papaveretum+hyoscine pretreatment (antecubital)	Papaveretum+hyoscine pretreatment (dorsum)	1	52	0.18 (0.04 to 0.74)	NA	124
Temperature of infused propofol (4°C/37°C):						
Propofol at room temperature+nafamostat	Propofol at room temperature	1	100	0.55 (0.40 to 0.74)	NA	135
Propofol at room temperature+lidocaine 10 mg	Propofol at room temperature	1	25	0.56 (0.29 to 1.08)	NA	132
Propofol at room temperature+lidocaine 20 mg	Propofol at room temperature	1	25	0.31 (0.13 to 0.75)	NA	132
Propofol at 4°C+lidocaine 10 mg	Propofol at 4°C	1	25	0.50 (0.25 to 1.00)	NA	132
Propofol at 4°C+lidocaine 20 mg	Propofol at 4°C	1	25	0.06 (0.01 to 0.44)	NA	132
Propofol at room temperature+lidocaine 40 mg	Propofol at 4°C+lidocaine 40 mg	1	30	0.42 (0.17 to 1.04)	NA	133
Propofol+lidocaine 0.1 mg/kg	Propofol at 4°C	1	58	1.59 (1.16 to 2.18)	NA	90
Propofol+lidocaine 0.2 mg/kg	Propofol at 4°C	1	57	1.80 (1.31 to 2.48)	NA	90
Lidocaine pretreatment followed by propofol at 4°C	Propofol at 4°C	1	40	0.28 (0.13 to 0.60)	NA	133
Drugs with venous occlusion (manual or tourniquet):	Without venous occlusion					
Antiemetics	None	2	200	0.54 (0.40 to 0.72)	77, 0.04	233;236
Barbiturates	None	2	112	0.20 (0.11 to 0.36)	85, 0.010	228;284
β blockers	None	2	160	0.49 (0.37 to 0.64)	22, 0.26	230;285
Kallikrein inhibitors	None	1	101	0.54 (0.38 to 0.76)	NA	286
Lidocaine	None	14	1052	0.29 (0.22 to 0.38)	59, <0.01	133;142;152;177;228-236
Ketamine	None	3	200	0.31 (0.22 to 0.44)	96, <0.001	231;284;287
NSAIDs	None	6	670	0.52 (0.44 to 0.60)	67, <0.001	177;199;201;232;288;289
Opioids	None	2	100	0.76 (0.60 to 0.97)	92, <0.001	229;284
Steroids	None	1	70	0.42 (0.27 to 0.66)	NA	234
Stimulants	None	1	50	0.95 (0.73 to 1.24)	NA	287
Opioids+lidocaine	Lidocaine+venous occlusion	1	64	0.13 (0.02 to 0.90)	NA	290
Opioids+lidocaine	Opioids+venous occlusion	1	63	0.11 (0.02 to 0.78)	NA	290
Lidocaine+ketamine+venous occlusion	Lidocaine+venous occlusion	1	64	0.22 (0.07 to 0.65)	NA	291
Lidocaine+ketamine+venous occlusion	Ketamine+venous occlusion	1	66	0.39 (0.15 to 0.99)	NA	291

NA=not applicable; NSAID=non-steroidal anti-inflammatory drug.
*Mantel Haenszel random effects model.

19 subcategories based on drug class—for example, antiemetics, local anaesthetics, benzodiazepines, barbiturates. Most of these drugs were partially successful in reducing the risk of pain from propofol injection.

A lidocaine-propofol admixture (25 trials) was the most effective intervention in this subcategory (0.40, 0.33 to 0.48, fig 3).[125 126 135 138 140-160] The funnel plot was, however, asymmetrical (arcsine transformation regression, t=−5.3, df=39, P<0.001) suggesting a strong small study effect or reporting bias for this intervention (fig 4). No other funnel plots were asymmetrical. A lidocaine-propofol admixture was of similar efficacy to pretreatment with lidocaine alone (24 studies) (0.47, 0.40 to 0.56, fig 5).[70 119 125 146 150 159 161-178]

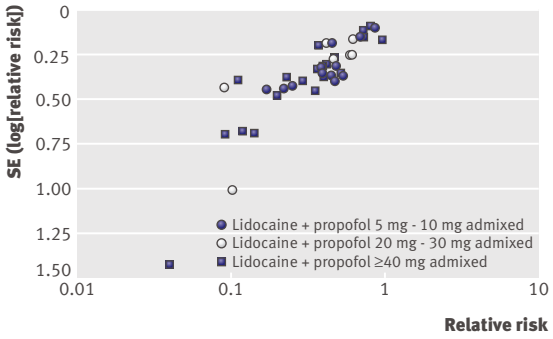

Fig 4 | Funnel plot of studies using lidocaine-propofol admixture

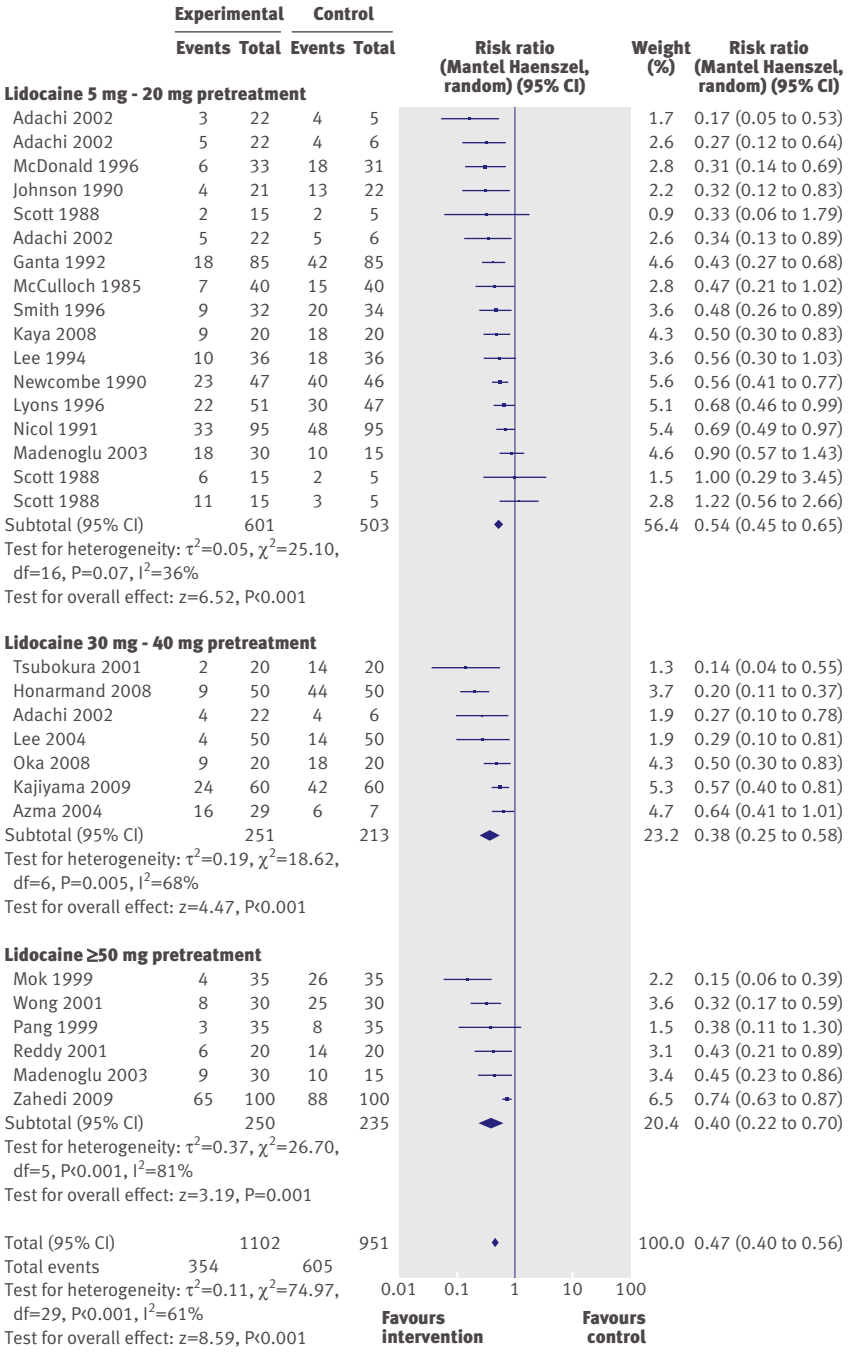

Fig 5 | Effect of pretreatment with lidocaine on risk of pain from propofol injection

Pretreatment with opioids showed analgesic benefit (0.49, 0.41 to 0.59, fig 6). Various opioids were studied: alfentanil (six studies),[179-184] remifentanil (n=5),[185-189] sufentanil (n=1),[187] fentanyl (n=3),[180 185 190] tramadol (n=3),[70 161 163] meperidine (pethidine) (n=3),[161 173 186] and butorphanol (n=1).[191] All of these opioids were successful in reducing pain from propofol injection.

Pretreatment with the N-methyl-D-aspartic acid antagonist ketamine was also effective in reducing the risk of pain from propofol injection (0.52, 0.46 to 0.57, fig 7).[164 168 192-196]

Pretreatment with non-steriodal anti-inflammatory drugs was also effective in seven trials (0.67, 0.49 to 0.91, fig 8). Flurbiprofen, diclofenac, and ketorolac were the primary agents explored for potential reduction of pain from propofol injection.[147 177 197-201]

Modified propofol formulations containing medium and long chain triglycerides compared with formulations containing long chain triglycerides were effective in 24 trials (0.75, 0.67 to 0.84, fig 9).[5 6 151 177 197 202-219] Combining trials that studied various combinations of standard and modified emulsion formulations with lidocaine had a similar effect (0.61, 0.44 to 0.84).[149 151 203 206 220-227]

Combined drug and non-drug category

The combined drug and non-drug category incorporated non-drug techniques such as site of injection,[119 123 124 126] alteration of temperature of propofol,[90 132 133 135] and venous occlusion (table 4). The most commonly studied intervention was venous occlusion in conjunction with various drugs, such as antiemetics, non-steroidal anti-inflammatory drugs, β blockers, lidocaine, and opioids; many combinations reduced the risk of pain from propofol injection. In this category pretreatment using lidocaine in conjunction with venous occlusion was the most effective intervention at preventing the pain from propofol injection (0.29, 0.22 to 0.38, fig 10).[133 142 152 177 228-236] One trial found that lidocaine applied ionophoretically was more effective than a sham application (0.31, 0.14 to 0.69).[237] Three trials found statistically significant results with modifications of propofol's temperature in combination with drugs such as lidocaine and nafamostat.[132 133 136]

Risk of bias assessment

Eight interventions statistically significantly reduced the pain from propofol injection. A sensitivity analysis to assess the potential effect of four criteria for the risk of bias assessment was carried out. When the point estimates or confidence intervals of the individual domains were compared with the overall point estimates, no appreciable difference occurred that would change the interpretation of the results (table 5).

Indirect comparisons

To be able to rank the interventions, a network approach was used to estimate indirect comparisons among effective interventions involving more than six studies.[11] Indirect treatment comparisons were estimated for the eight pairwise (intervention versus control) statistically significant interventions; the data were derived from 167 treatment arms in 101 studies. These eight interventions were included as moderators in a mixed effects metaregression (table 6). An omnibus test for inclusion of the moderators was significant ($F=46.5_{8, 159}$, $P<0.001$) and each individual regression coefficient was significant (t statistics, $P<0.05$ for all interventions). While the residual heterogeneity ($\tau^2=0.10$) remained significant ($\chi^2=402$, df=159, $P<0.001$), about 44% of the residual heterogeneity had been accounted for by the inclusion of the eight

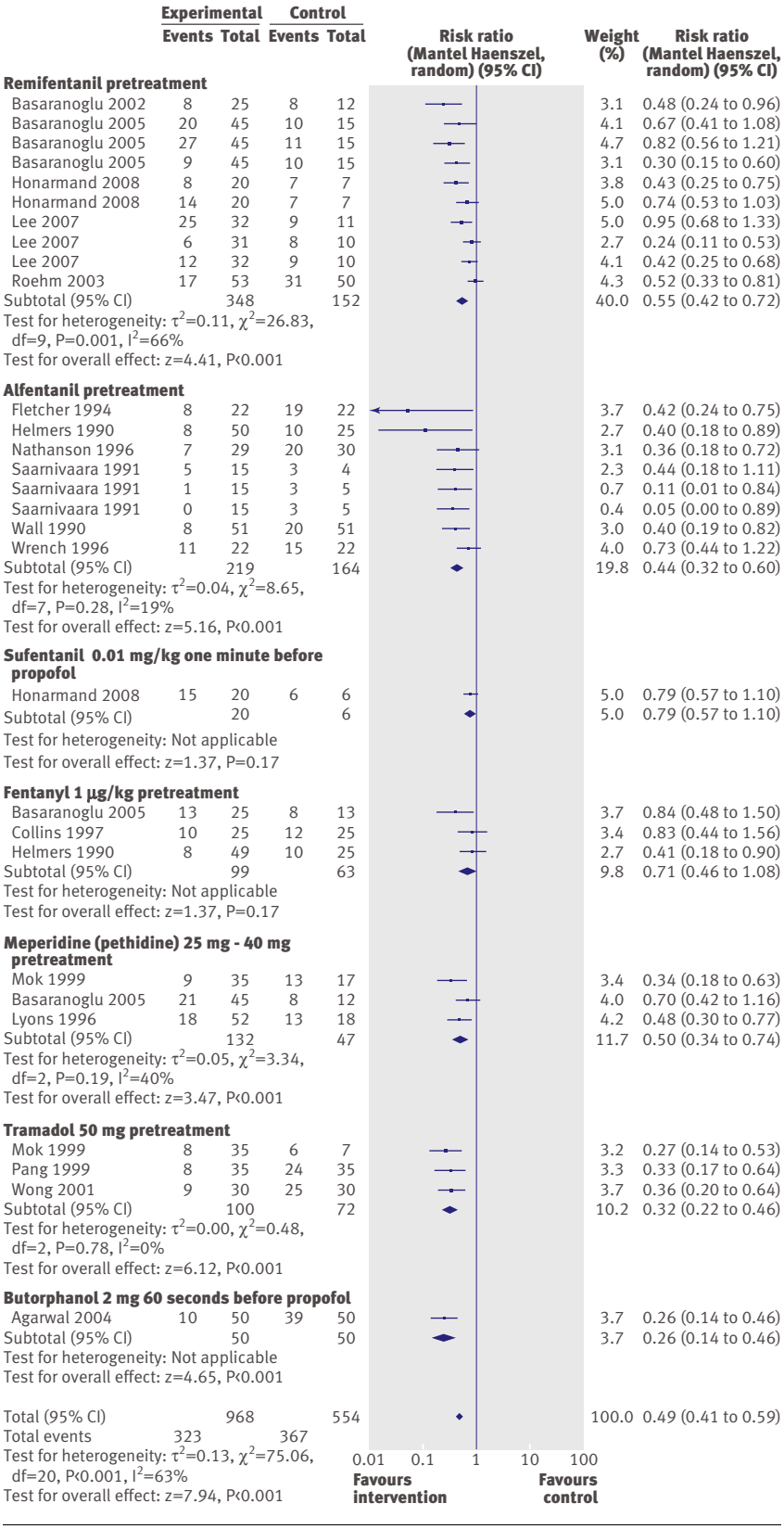

Fig 6 | Effect of pretreatment with opioids on risk of pain from propofol injection

moderators in the model; the Akaike information criterion was also reduced in the full model.

The relative risk of using an antecubital vein was lower than for six of the other interventions, with the indirect relative risks ranging from 0.19 (modified propofol formulation) to 0.34 (lidocaine-propofol admixture). Pretreatment using lidocaine in conjunction with venous occlusion also had a lower relative risk than six of the other interventions, with the indirect relative risks ranging from 0.39 (modified propofol formulation) to 0.69 (lidocaine-propofol admixture). Although the indirect relative risk for using an antecubital vein compared with pretreatment using lidocaine in conjunction with venous occlusion was 0.50, the 95% confidence interval extended beyond the identity line.

The risk of pain was similarly reduced for five interventions (lidocaine-propofol admixture, and pretreatment with lidocaine, opioids, ketamine, and non-steroidal anti-inflammatory drugs), with direct relative risks varying from 0.43 to 0.67. Confidence intervals for nine of the 10 indirect relative risks between the five interventions were non-significant (table 6). Six interventions had lower indirect relative risks compared with a modified propofol formulation.

DISCUSSION

About 60% of patients experience pain on injection with standard propofol alone—that is, without any preventive measures. A previous systematic review and meta-analysis identified pretreatment using lidocaine (lignocaine) in conjunction with venous occlusion using a tourniquet to be the most efficacious intervention to reduce pain from propofol injection.[2] Since then more than 100 randomised controlled trials have been published on the topic. Our systematic review and meta-analysis confirms the efficacy of the previously suggested technique (relative risk 0.29). However, selecting an antecubital vein instead of a hand vein was numerically the most efficacious intervention (relative risk 0.14). In addition, we identified six other efficacious interventions that are commonly used—namely, lidocaine-propofol admixture; pretreatment using lidocaine (without venous occlusion), opioids, non-steroidal anti-inflammatory drugs, or ketamine; and a propofol emulsion containing medium and long chain triglycerides. Furthermore, we carried out indirect comparisons across the meta-analyses and found that choosing the antecubital vein and venous occlusion along with pretreatment using lidocaine were similarly efficacious and clearly superior to the other six interventions.

The results of this analysis show that injection of propofol through an antecubital vein is one of the most effective interventions to reduce associated pain. From a physiological standpoint, differences in vein diameter, flow rate, and endothelial structure might account for the reduction in pain. Presuming that propofol is injected mid-stream into the lumen of the vein, the larger diameter of and faster flow rate through the antecubital vein will minimise the extent to which a high concentration of propofol comes into contact

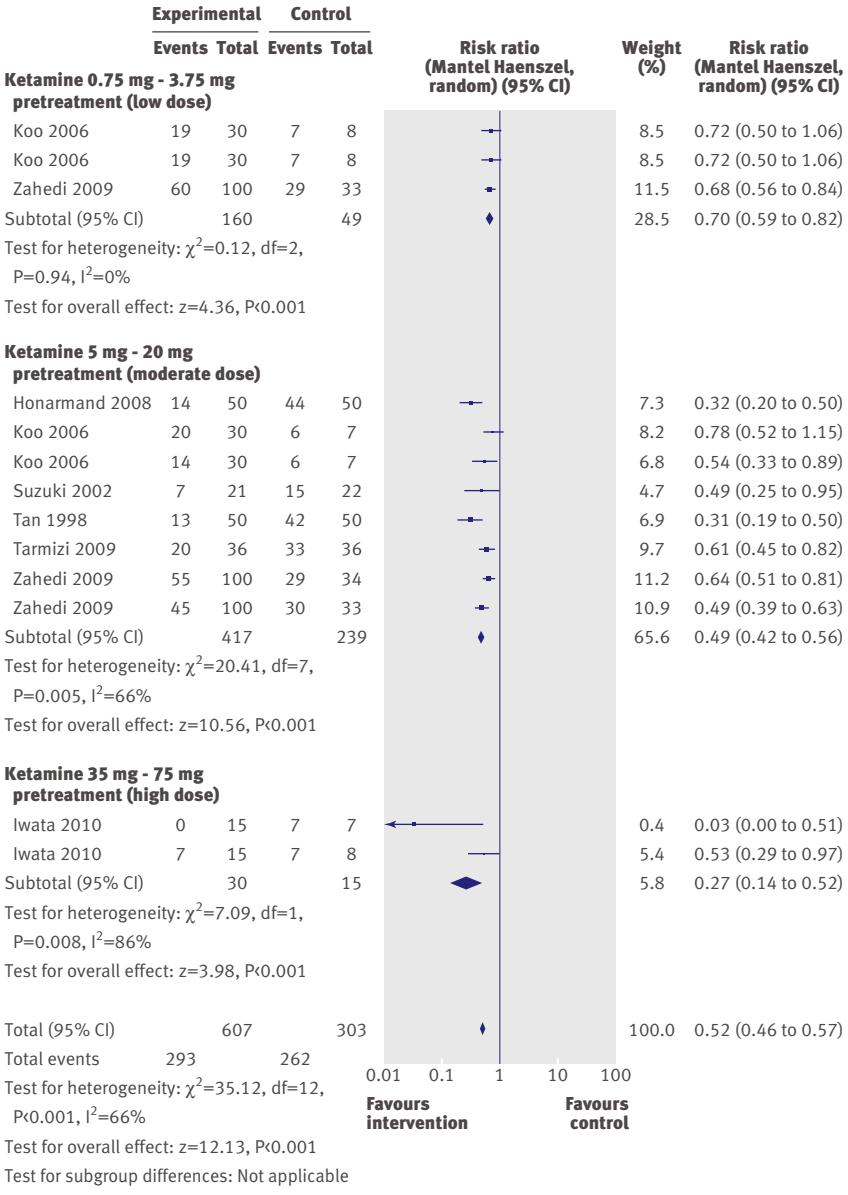

Fig 7 | Effect of pretreatment with ketamine on risk of pain from propofol injection

with the sensitive endothelial wall. Alternatively, propofol may be buffered more effectively when more blood is available to dissipate and mask the "full effect" of the bolus. Additionally, the composition of nociceptors along the endothelial wall might differ between the smaller veins of the hand and the larger antecubital veins.[119 139 238 239] In contrast to careful selection of veins, other non-drug interventions—for example, both cold and warm propofol, adjusting the speed of intravenous carrier fluid, and microfiltration—were disappointingly ineffective approaches for alleviating pain from propofol injection.

The other similarly effective intervention was a combination of a drug and non-drug techniques—that is, pretreatment using lidocaine in conjunction with venous occlusion before injection. Although this has been considered the most efficacious technique, it has not become standard.[2] A reason for this may be the additional procedural steps involved in the intervention, leading to some delay when swift induction is expected. In addition, venous occlusion has also been paired with many other drugs (for example, antiemetics, non-steroidal anti-inflammatory drugs, opioids) and was found to have some measurable success, albeit less so than when venous occlusion was combined with pretreatment using lidocaine. Although some of these combinations of interventions reached statistical significance, they were generally only investigated in a few studies, which makes it difficult to draw meaningful conclusions.

Although pretreatment of a hand vein using lidocaine in conjunction with proximal venous occlusion seems as effective as using an antecubital vein, clinicians may prefer the antecubital vein because it is an effective route and simple to use.

Similarly, of the drug interventions, a lidocaine-propofol admixture was similarly efficacious when compared with pretreatment using lidocaine alone. Both interventions were, however, considerably less efficacious than pretreatment with lidocaine in conjunction with venous occlusion. Interestingly, in the newer studies a trend was towards using a lidocaine-propofol admixture as opposed to propofol alone as the control group, suggesting that this clinical practice has become widely spread. Additionally, the funnel plot for the lidocaine-propofol admixture showed significant asymmetry (fig 4).[10 240] Although this intervention with lidocaine may be efficacious, its treatment effect may be well overestimated.

Our analysis of almost 1500 patients showed that pretreatment with opioids resulted in a relative risk of about 0.50. Thus, unless contraindicated otherwise, it seems reasonable to use opioids as standard pretreatment several minutes before induction.

Multiple trials investigated a variety of propofol formulations, such as lipid-free formulations, modified emulsion formulations, and propofol containing bismuth. Of these, the most commonly studied emulsions, those containing medium and long chain triglycerides, were compared with the conventional emulsions containing long chain triglyceride (2344 patients, 24 studies), with a relative risk of 0.75 for emulsions containing medium and long chain triglycerides.

Other promising drug interventions were pretreatment with ketamine and with non-steroidal anti-inflammatory drugs. Pretreatment with either of these drugs should not only decrease the pain from propofol injection but also reduce postoperative pain, postoperative nausea and vomiting, and the need for postoperative opioids.[241 242] However, diclofenac sodium is itself associated with pain on injection, which may lead to thrombophlebitis.[62 243] Although this may be avoided by using a newer formulation, dilution, or slow intravenous infusion, the pain on injection using diclofenac limits its use for reducing the pain from propofol injection.

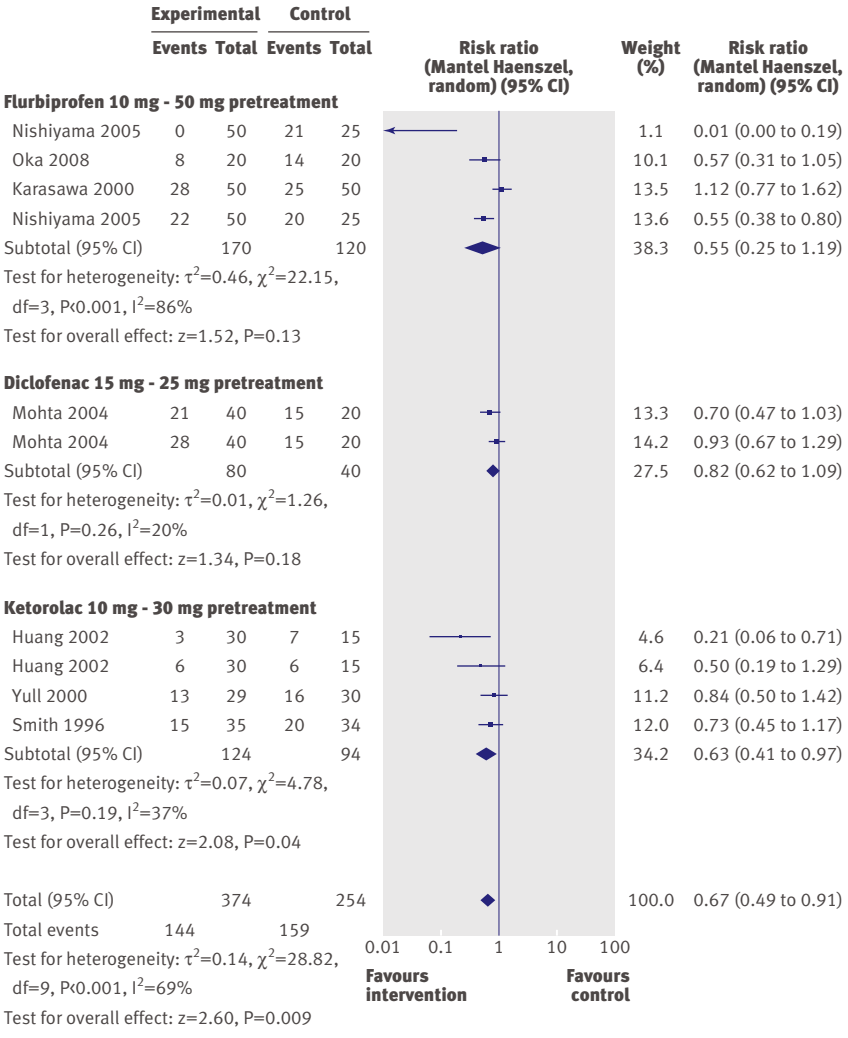

Fig 8 | Effect of pretreatment with non-steroidal anti-inflammatory drugs on risk of pain from propofol injection

Clinical implications

Based on the comparisons carried out here, it seems that among the wide arrays of interventions tested, eight had sufficient evidence of benefit. When interventions seem similarly efficacious, choices for intervention can be made on factors such as cost, personal choice, and simplicity of application.

Our results of direct and indirect comparisons suggest a possible strategy that is both efficacious and easy to apply in clinical practice (fig 11). Since opioids are used commonly as part of a balanced anaesthesia protocol, it seems reasonable to use them as routine premedication in preparation for induction for all three options, as they halve the risk of pain from propofol injection (relative risk 0.50). We do not recommend the use of non-steroidal anti-inflammatory drugs as the results for these agents were heterogeneous and some themselves cause pain on injection. One approach could be to use an antecubital vein, whenever practicable, with its relative risk reduction of about 85%. Based on the assumption that interventions of independent pathways work independently,[244] the risk of pain on injection is likely to be only 5% when preoperative opioids are combined with the antecubital approach (60%×0.49×0.14=4.1%). In other words, further interventions are unlikely to benefit more than 1 out of 20 patients, thereby additional interventions would only provide limited additional benefit from a clinical standpoint.

As an intravenous line in the antecubital vein may be occluded when the elbow is flexed, unintentional extravasations may not be detected as quickly as when the dorsum of the hand is used. Therefore when intravenous placement into the antecubital vein is challenging, we consider a fair alternative to be the hand vein with preoperative opioids plus lidocaine in conjunction with venous occlusion as this would also bring the risk down to less than 10% (60%×0.49×0.29=8.5%). Notably, a lidocaine-propofol admixture was also statistically significantly superior to placebo and is probably the most commonly used approach to reduce the pain from propofol injection. Owing to possible publication bias, however, the "true treatment effect" is unclear so we prefer similarly efficacious methods that have no evidence of publication bias. The other practical alternative could be to use preoperative opioids in

Table 5 | Sensitivity analysis to assess potential effect of four criteria for risk of bias assessment in studies with statistically significant results for interventions to reduce the pain from propofol injection

Intervention	Overall relative risk (95% CI) (No of studies)	Relative risk* (95% CI) (No of studies)			
		Sequence generation	Allocation concealment	Blinding	Completeness of outcome data reported
Antecubital versus hand vein	0.14 (0.07 to 0.30) (6)	0.14 (0.05 to 0.36) (1)	0.18 (0.07 to 0.46) (4)	0.05 (0.00 to 0.79) (1)	0.14 (0.07 to 0.30) (6)
Lidocaine pretreatment+venous occlusion	0.29 (0.22 to 0.38) (14)	0.27 (0.19 to 0.37) (9)	0.27 (0.20 to 0.35) (11)	0.29 (0.22 to 0.39) (13)	0.27 (0.21 to 0.35) (13)
Lidocaine-propofol admixture	0.40 (0.33 to 0.48) (25)	0.45 (0.31 to 0.64) (7)	0.45 (0.31 to 0.64) (7)	0.41 (0.33 to 0.50) (19)	0.41 (0.33 to 0.50) (20)
Lidocaine pretreatment	0.47 (0.40 to 0.56) (24)	0.39 (0.29 to 0.53) (9)	0.44 (0.32 to 0.60) (10)	0.44 (0.35 to 0.56) (16)	0.52 (0.43 to 0.61) (21)
Opioid pretreatment	0.49 (0.41 to 0.59) (17)	0.47 (0.34 to 0.66) (6)	0.47 (0.34 to 0.66) (6)	0.50 (0.41 to 0.59) (16)	0.48 (0.40 to 0.58) (16)
Ketamine pretreatment	0.56 (0.47 to 0.67) (7)	0.34 (0.15 to 0.74) (3)	0.34 (0.15 to 0.74) (1)	0.52 (0.46 to 0.57) (7)	0.55 (0.45 to 0.69) (5)
NSAID pretreatment	0.67 (0.49 to 0.91) (7)	0.57 (0.36 to 0.91) (4)	0.57 (0.36 to 0.91) (5)	0.79 (0.62 to 1.01) (5)	0.67 (0.41 to 0.97) (7)
Emulsion of medium and long chain trigylcerides *v* long chain triglycerides	0.75 (0.67 to 0.84) (24)	0.85 (0.67 to 1.06) (11)	0.84 (0.68 to 1.04) (12)	0.76 (0.68 to 0.84) (21)	0.73 (0.64 to 0.83) (21)

NSAID=non-steroidal anti-inflammatory drug.
*Mantel Haenszel random effects model.

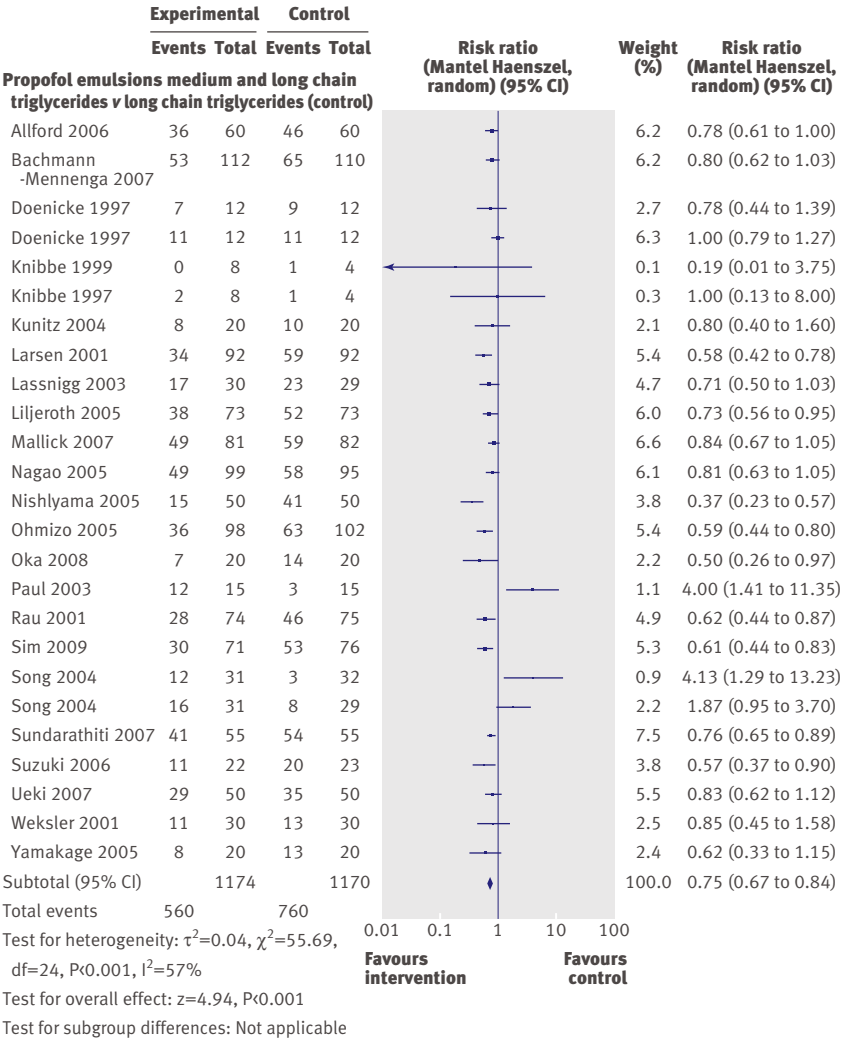

Fig 9 | Effect of propofol emulsions containing medium and long chain triglycerides compared with those containing long chain trigylcerides on risk of pain from propofol injection

conjunction with pretreatment using lidocaine or ketamine before the injection of a propofol emulsion containing medium and long chain triglycerides, thereby also reducing the risk of pain to about 10-12% (60%×0.49×0.47×0.75=10.3%) or 12% (60%×0.49×0.56×0.75=12.3%). Nevertheless, these estimates of multiplicative treatment effects are based on the assumption of independence and strictly speaking require confirmation in randomised controlled trials.

Limitations of the study

A range of other techniques reached statistical significance in a limited number of studies (often only one or two) and some of them lacked biological plausibility, such as the efficacy reported for antiemetics, cholinesterase inhibitors, antihistamines, stimulants, and combinations of interventions. Further research is needed to verify or refute these results and, if these interventions are truly efficacious, it will be essential to uncover underlying mechanisms. Furthermore, assessment of the intensity of pain score as an additional outcome was unachievable.

Conclusions

Unless contraindicated we recommend the routine use of a small dose of opioids before induction of anaesthesia using propofol injection in all patients. On the basis of efficacy and convenience we also recommend using an antecubital vein instead of a hand vein. If the hand vein is the site of injection, we recommend pretreatment using lidocaine in conjunction with venous occlusion, or a combined intervention such as pretreatment with ketamine or lidocaine before injection of a propofol emulsion containing medium and long chain triglycerides.

Table 6 | Indirect comparisons between efficacious interventions to reduce pain from propofol injection

	Relative risk (95% CI)						
Intervention *v* control	Antecubital vein	Lidocaine pretreatment+venous occlusion	Lidocaine combination	Lidocaine pretreatment	Opioids pretreatment	Ketamine pretreatment	NSAID pretreatment
Antecubital vein 0.15 (0.07 to 0.33)***	1.00	—	—	—	—	—	—
Lidocaine pretreatment+venous occlusion 0.29 (0.22 to 0.39)***	0.50 (0.22 to 1.16)	1.00	—	—	—	—	—
Lidocaine-propofol admixture 0.43 (0.37 to 0.50)***	0.34 (0.15 to 0.77)*	0.69 (0.50 to 0.94)*	1.00	—	—	—	—
Lidocaine pretreatment 0.47 (0.39 to 0.57)***	0.32 (0.14 to 0.71)**	0.63 (0.45 to 0.88)**	0.92 (0.72 to 1.17)	1.00	—	—	—
Opioid pretreatment 0.51 (0.42 to 0.61)***	0.29 (0.13 to 0.66)**	0.58 (0.42 to 0.81)**	0.85 (0.66 to 1.08)	0.92 (0.71 to 1.20)	1.00	—	—
Ketamine pretreatment 0.55 (0.44 to 0.70)***	0.27 (0.12 to 0.61)**	0.53 (0.37 to 0.77)***	0.78 (0.59 to 1.03)	0.85 (0.63 to 1.15)	0.92 (0.68 to 1.24)	1.00	—
NSAID pretreatment 0.67 (0.49 to 0.91)*	0.22 (0.10 to 0.52)***	0.44 (0.29 to 0.66)***	0.64 (0.45 to 0.90)*	0.70 (0.49 to 1.00)	0.76 (0.53 to 1.08)	0.82 (0.56 to 1.21)	1.00
Emulsions with medium and long chain triglycerides *v* long chain triglycerides 0.76 (0.64 to 0.91)**	0.19 (0.09 to 0.44)***	0.39 (0.28 to 0.53)***	0.56 (0.44 to 0.71)***	0.61 (0.47 to 0.79)***	0.66 (0.51 to 0.86)**	0.72 (0.54 to 0.97)*	0.88 (0.62 to 1.25)

NSAID=non-steroidal anti-inflammatory drug.
The analysis was done in R package metafor using restricted maximum likelihood rather than Mantel Haenszel estimation in Review Manager. As there are slight differences in partitioning of control group event rates to avoid unit of analysis errors and because Mantel Haenszel estimation is closed form whereas restricted maximum likelihood is iterative, there are slight differences of the direct relative risks from values displayed in table 1.
*P<0.05; **P<0.01; ***P<0.001.

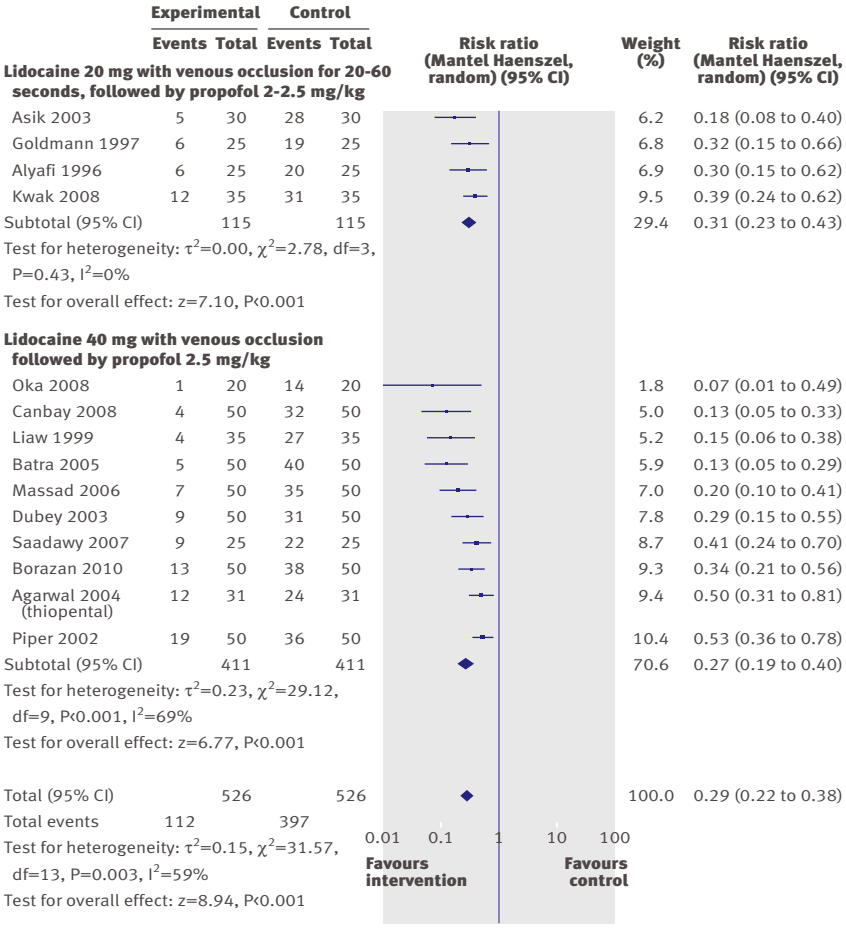

Fig 10 | Effect of pretreatment using lidocaine in conjunction with venous occlusion or no venous occlusion on risk of pain from propofol injection

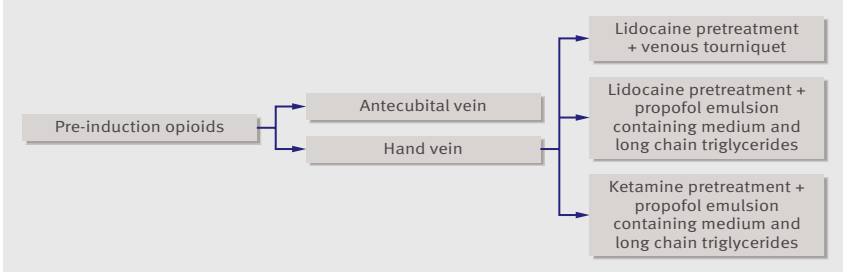

Fig 11 | Possible simple strategy to minimise pain from propofol injection

WHAT IS ALREADY KNOWN ON THIS TOPIC

Pretreatment with lidocaine (lignocaine) in conjunction with venous occlusion has been suggested as the best intervention to reduce pain from propofol injection

This technique failed to gain widespread popularity and the search for alternative interventions continues

WHAT THIS STUDY ADDS

Using an antecubital vein instead of a hand vein is a simple and effective way to avoid the pain from propofol injection

If the hand vein is chosen, pretreatment using lidocaine in conjunction with venous occlusion is equally efficacious, although not widely used

A third option could be the combination of "less efficacious interventions," such as using a modified propofol emulsion in conjunction with pretreatment of the hand vein using lidocaine or ketamine

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Contributors: VK, LJ, YYS, OR, and CCA wrote the study protocol. LJ and VK collected and collated the data. CCA and NLP provided statistical expertise. CCA, LJ, and NLP analysed and interpreted the data. LJ, YYS, EG, CH, CCA, and NLP drafted the article. LJ, EG, YYS, CH, CCA, OR, and NLP critically revised the article for important intellectual content. LJ, EG, YYS, CH, CCA, and NLP provided administrative, technical, or logistic support. All authors approved the final article, had full access to all the data (including statistical reports and tables), and can take responsibility for the integrity of the data and the accuracy of the data analysis. CCA, LJ, and NLP are the guarantors.

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Ethical approval: Not required.

Data sharing: The technical appendix, statistical code, and dataset are available from the corresponding author at apfelc@anesthesia.ucsf.edu.

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