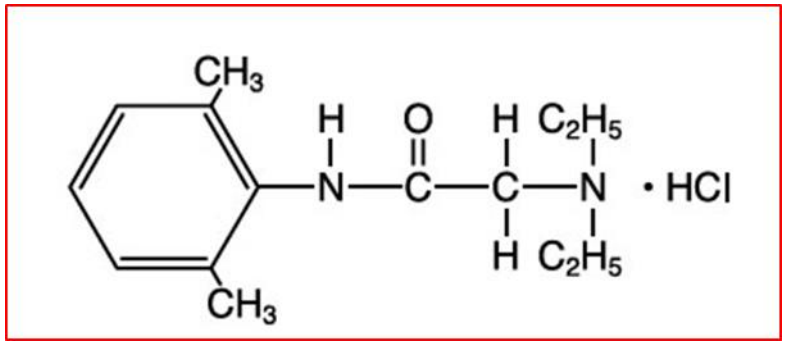
Intravenous lidocaine for postoperative pain and recovery



Andrew Smith

Royal Lancaster Infirmary, UK

11 November 2021

Declaration

- Co-ordinating Editor, Cochrane Anaesthesia Review Group
- Advisory Member, RCoA/AAGBI Safe Anaesthesia Liaison Group
- Not a clinical expert!

Outline

1. Is intravenous lidocaine effective?
2. Is it safe?
3. How does its unlicensed status affect its use?
4. Present safety statement and subsequent reactions

1 Is lidocaine effective?

Weibel S et al *Cochrane Database of Systematic Reviews* 2018; Issue 6

Is lidocaine effective?

- I.v. lidocaine *vs.* control or placebo infusion
- Updated literature search
- RCTs only
- Risk of bias appraisal and GRADE
- Random effects meta-analysis plus prediction intervals (95% PI)
- Pain at rest (early, intermediate, late).

  GI recovery. Opioid use. Nausea. Adverse events.

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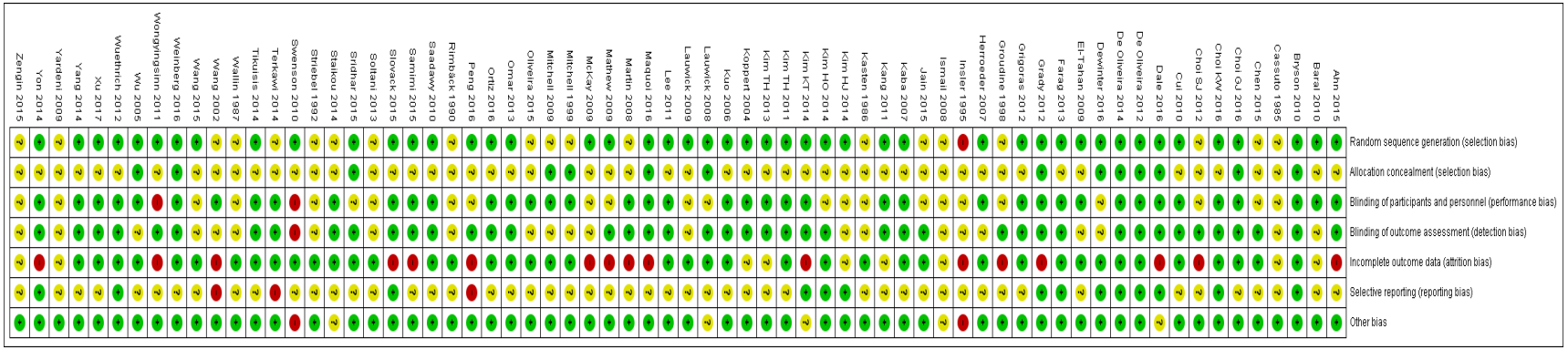
Results

- 68 RCTs, 4524 participants

Risk of bias


Ahn 2015
Baral 2010
Bryson 2010
Cassuto 1985
Chen 2015
Choi GJ 2016
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Dale 2016
De Oliveira 2012
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El-Tahan 2009
Farag 2013
Grady 2012
Grigoras 2012
Groudine 1998
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Ismail 2008
Jain 2015
Kaba 2007
Kang 2011
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Koppert 2004
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Lee 2011
Maquoi 2016
Martin 2008
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McKay 2009
Mitchell 1999
Mitchell 2009
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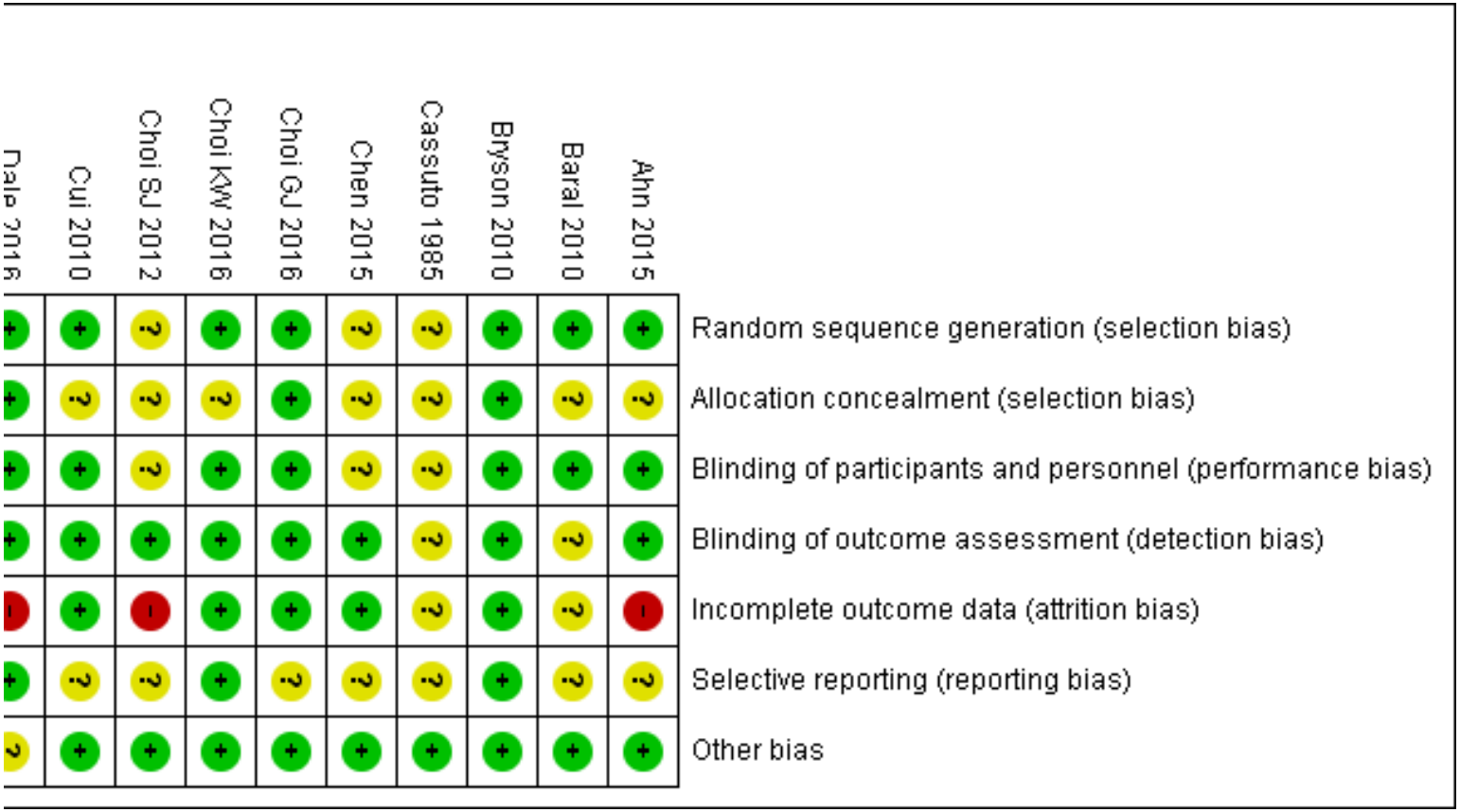
Ortiz 2016
Peng 2016
Rimbäck 1990
Saadawy 2010
Samimi 2015
Slovack 2015
Soltani 2013
Sridhar 2015
Staikou 2014
Striebel 1992
Swenson 2010
Terkawi 2014
Tikuisis 2014
Wallin 1987
Wang 2002
Wang 2015
Weinberg 2016
Wongyingsinn 2011
Wu 2005
Wuethrich 2012
Xu 2017
Yang 2014
Yardeni 2009
Yon 2014
Zengin 2015
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Risk of bias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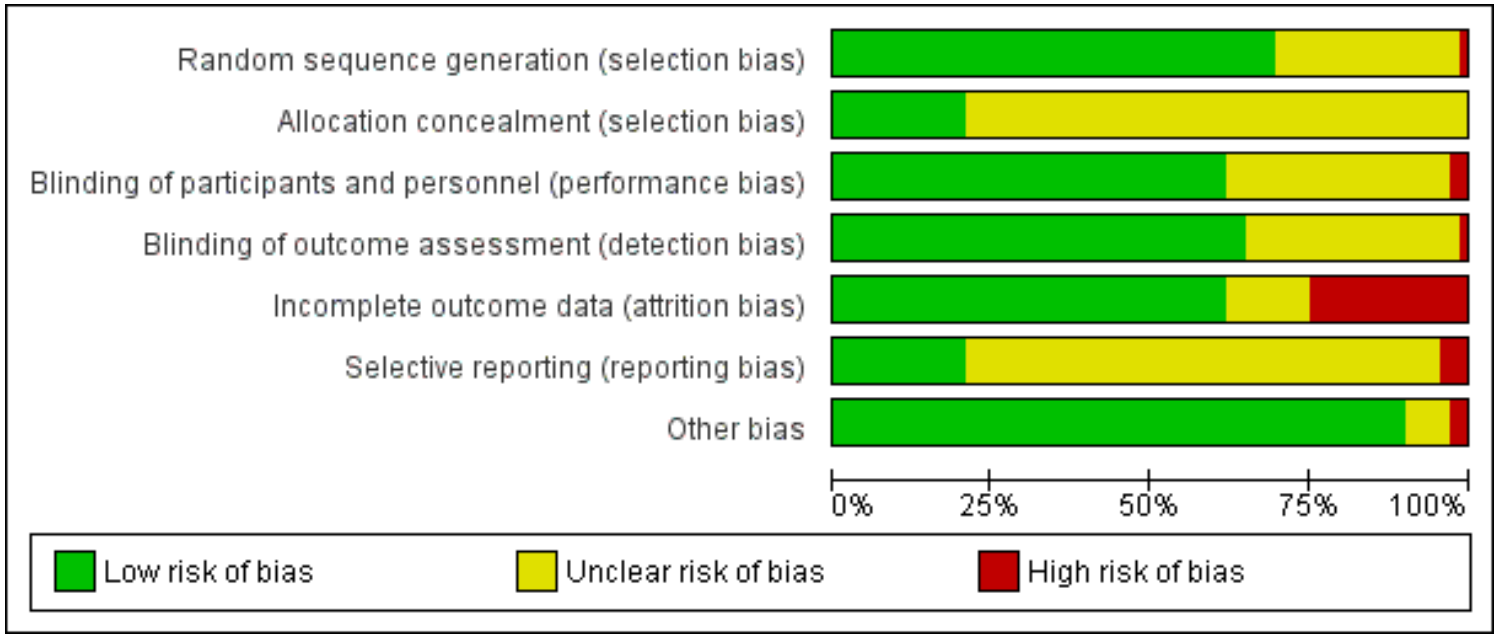
Risk of bias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Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Review: Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults
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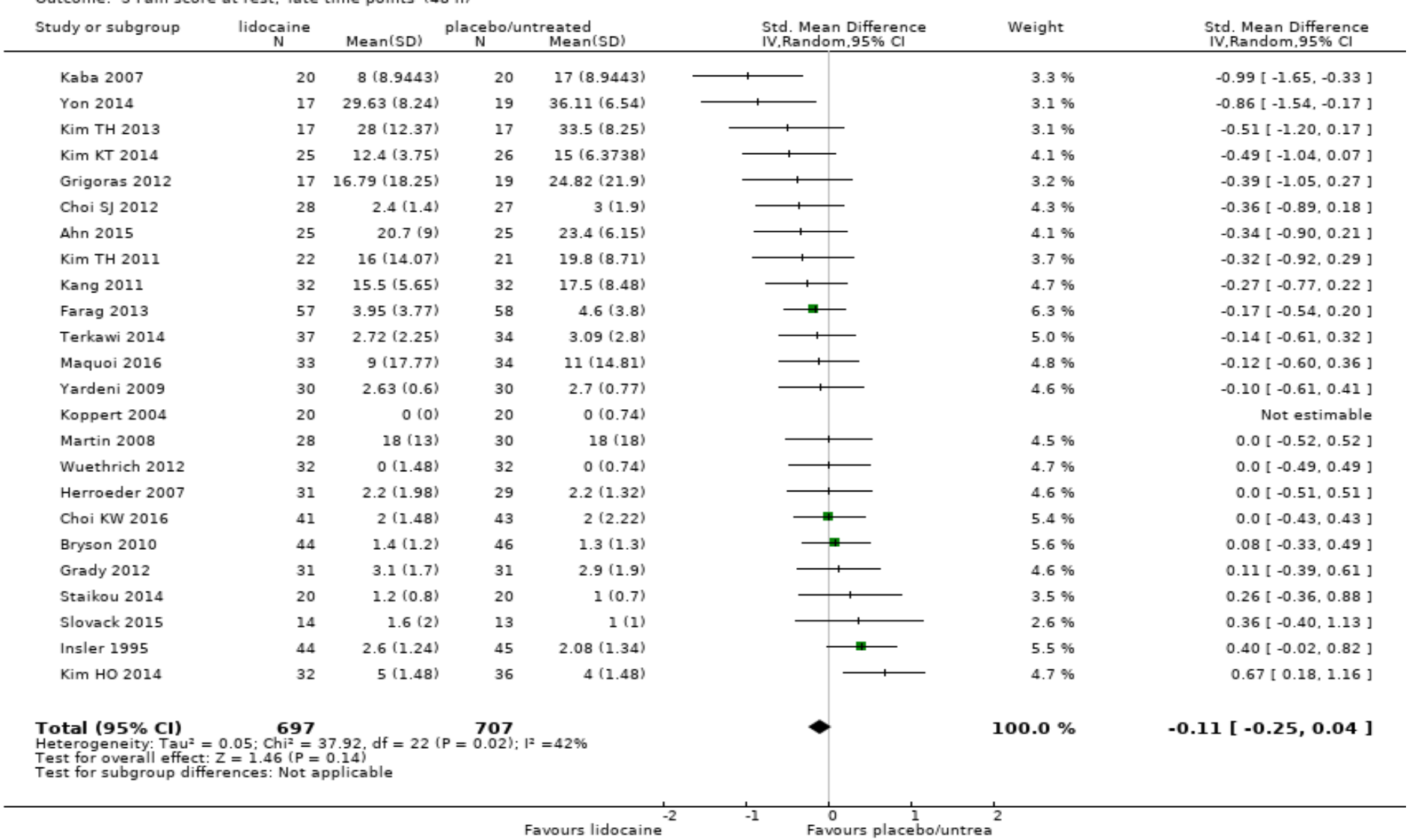

Heterogeneity: Tau² = 0.05; Chi² = 37.92, df = 22 (P = 0.02); I² =42%
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Test for subgroup differences: Not applicable

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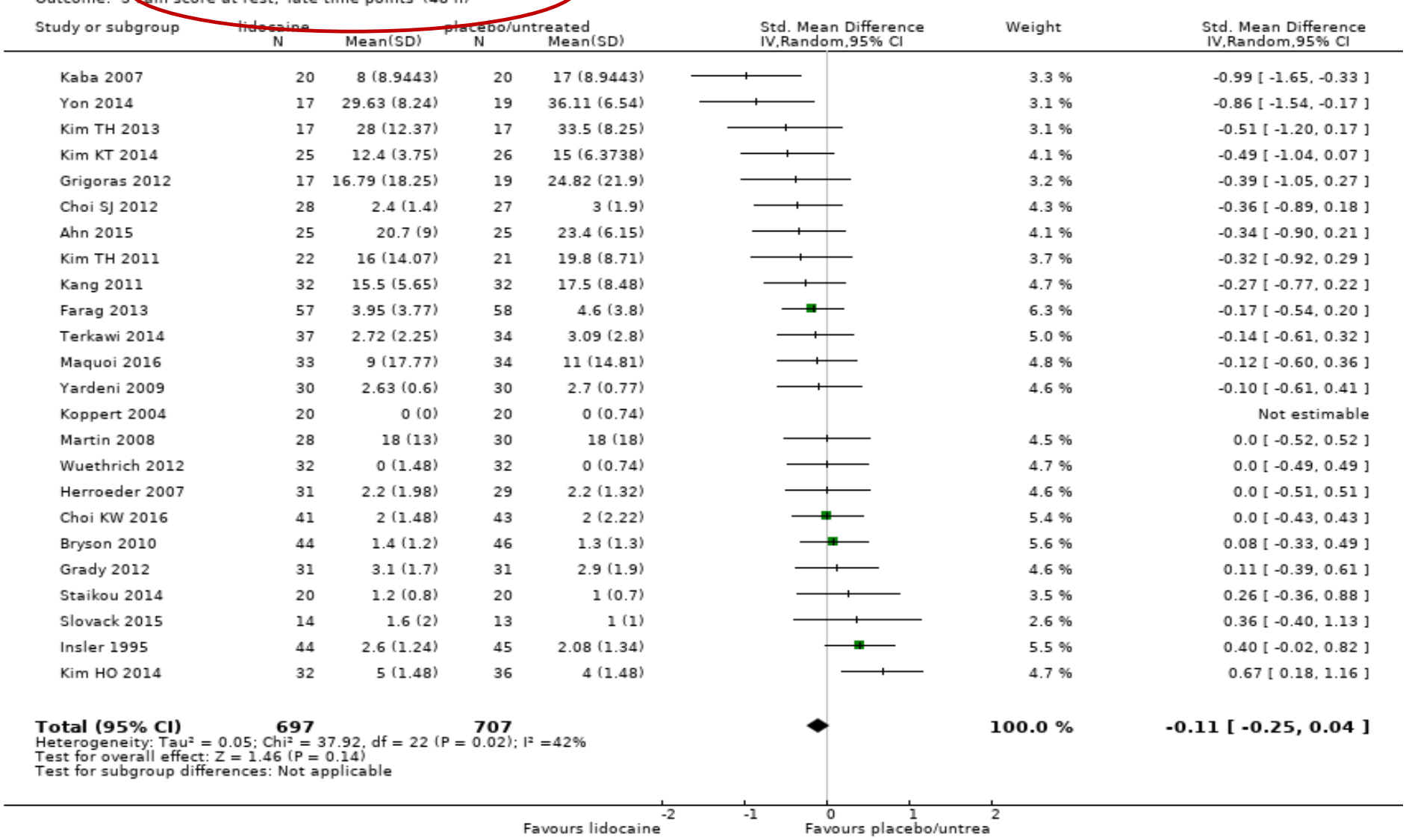

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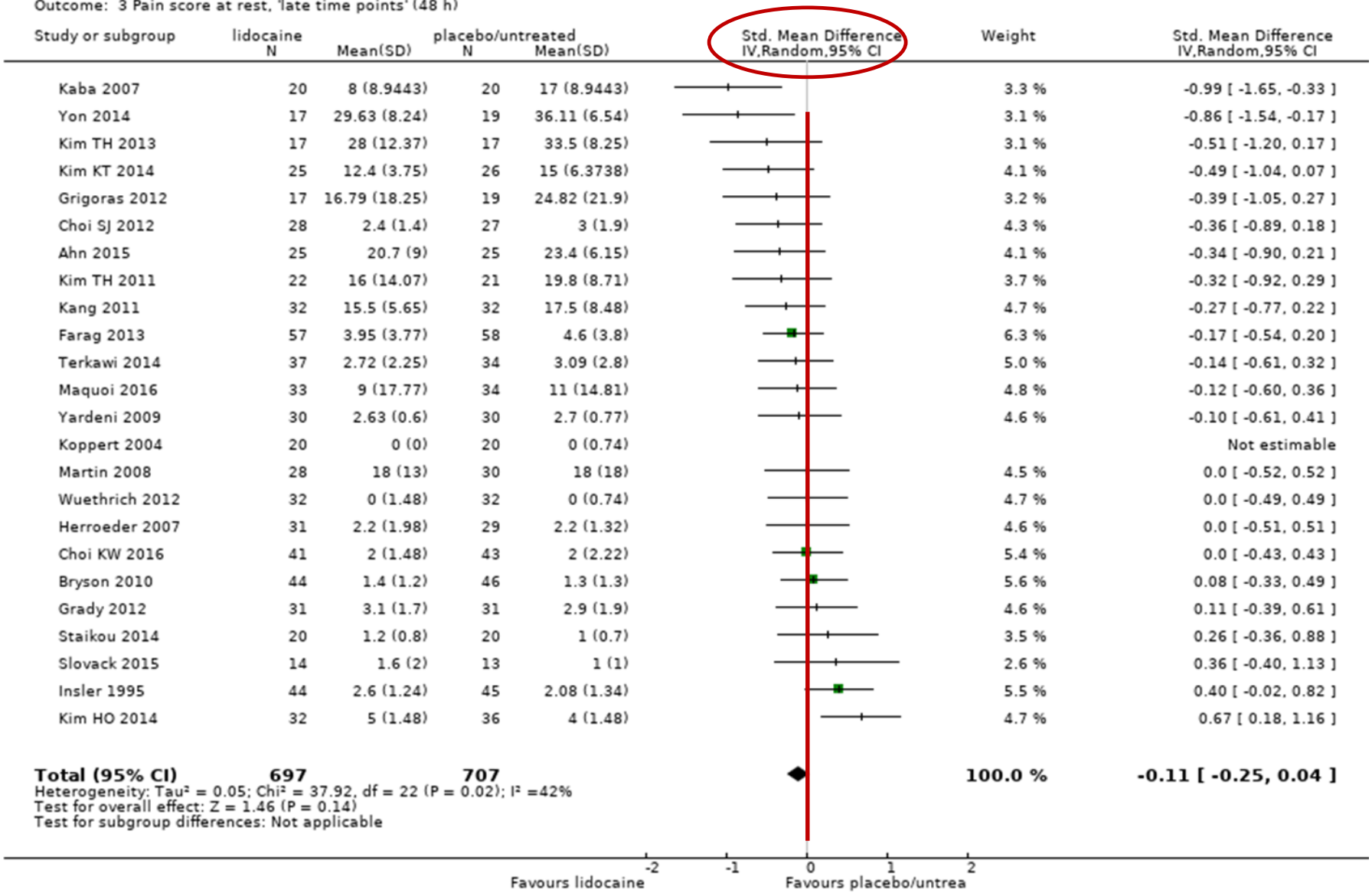

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Study or subgroup	lidocaine N	Mean(SD)	placebo/untreated N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Kaba 2007	20	8 (8.9443)	20	17 (8.9443)		3.3 %	-0.99 [-1.65, -0.33]
Yon 2014	17	29.63 (8.24)	19	36.11 (6.54)		3.1 %	-0.86 [-1.54, -0.17]
Kim TH 2013	17	28 (12.37)	17	33.5 (8.25)		3.1 %	-0.51 [-1.20, 0.17]
Kim KT 2014	25	12.4 (3.75)	26	15 (6.3738)		4.1 %	-0.49 [-1.04, 0.07]
Grigoras 2012	17	16.79 (18.25)	19	24.82 (21.9)		3.2 %	-0.39 [-1.05, 0.27]
Choi SJ 2012	28	2.4 (1.4)	27	3 (1.9)		4.3 %	-0.36 [-0.89, 0.18]
Ahn 2015	25	20.7 (9)	25	23.4 (6.15)		4.1 %	-0.34 [-0.90, 0.21]
Kim TH 2011	22	16 (14.07)	21	19.8 (8.71)		3.7 %	-0.32 [-0.92, 0.29]
Kang 2011	32	15.5 (5.65)	32	17.5 (8.48)		4.7 %	-0.27 [-0.77, 0.22]
Farag 2013	57	3.95 (3.77)	58	4.6 (3.8)		6.3 %	-0.17 [-0.54, 0.20]
Terkawi 2014	37	2.72 (2.25)	34	3.09 (2.8)		5.0 %	-0.14 [-0.61, 0.32]
Maquoi 2016	33	9 (17.77)	34	11 (14.81)		4.8 %	-0.12 [-0.60, 0.36]
Yardeni 2009	30	2.63 (0.6)	30	2.7 (0.77)		4.6 %	-0.10 [-0.61, 0.41]
Koppert 2004	20	0 (0)	20	0 (0.74)			Not estimable
Martin 2008	28	18 (13)	30	18 (18)		4.5 %	0.0 [-0.52, 0.52]
Wuethrich 2012	32	0 (1.48)	32	0 (0.74)		4.7 %	0.0 [-0.49, 0.49]
Herroeder 2007	31	2.2 (1.98)	29	2.2 (1.32)		4.6 %	0.0 [-0.51, 0.51]
Choi KW 2016	41	2 (1.48)	43	2 (2.22)		5.4 %	0.0 [-0.43, 0.43]
Bryson 2010	44	1.4 (1.2)	46	1.3 (1.3)		5.6 %	0.08 [-0.33, 0.49]
Grady 2012	31	3.1 (1.7)	31	2.9 (1.9)		4.6 %	0.11 [-0.39, 0.61]
Staikou 2014	20	1.2 (0.8)	20	1 (0.7)		3.5 %	0.26 [-0.36, 0.88]
Slovack 2015	14	1.6 (2)	13	1 (1)		2.6 %	0.36 [-0.40, 1.13]
Insler 1995	44	2.6 (1.24)	45	2.08 (1.34)		5.5 %	0.40 [-0.02, 0.82]
Kim HO 2014	32	5 (1.48)	36	4 (1.48)		4.7 %	0.67 [0.18, 1.16]
Total (95% CI)	**697**		**707**			**100.0 %**	**-0.11 [-0.25, 0.04]**

Heterogeneity: Tau² = 0.05; Chi² = 37.92, df = 22 (P = 0.02); I² =42%
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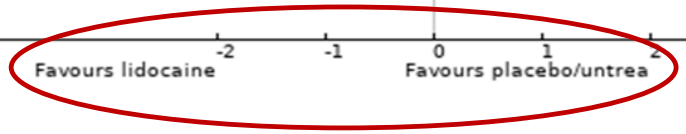

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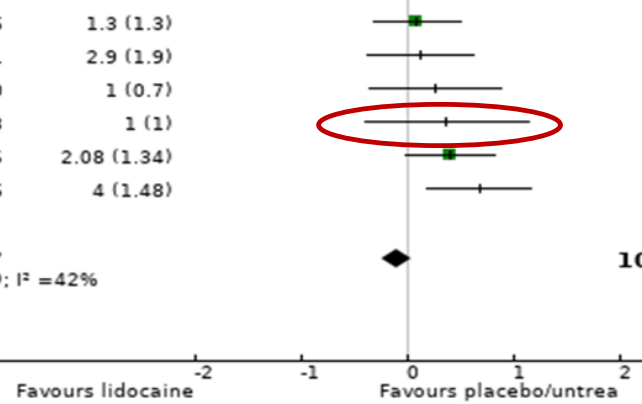

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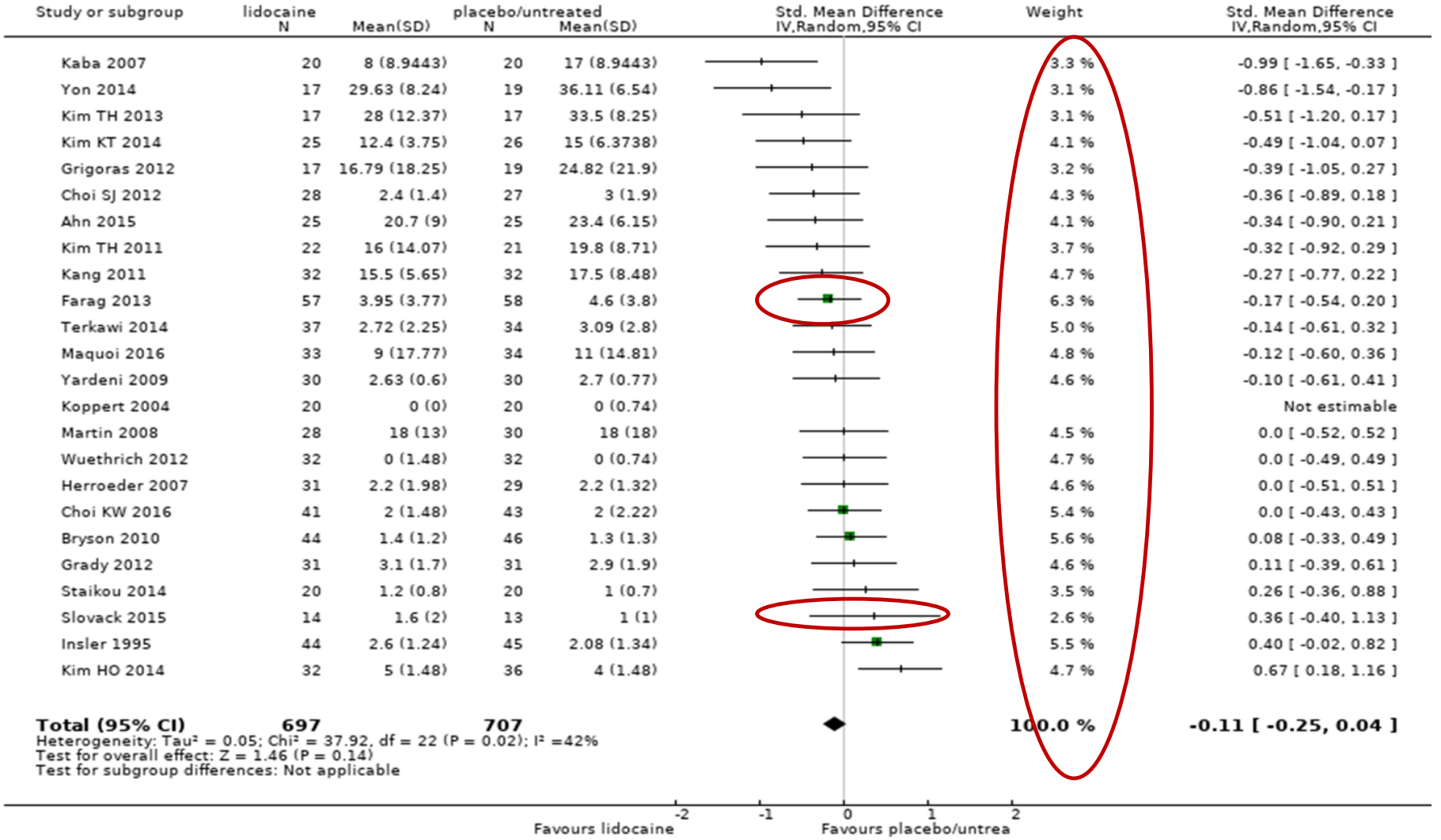

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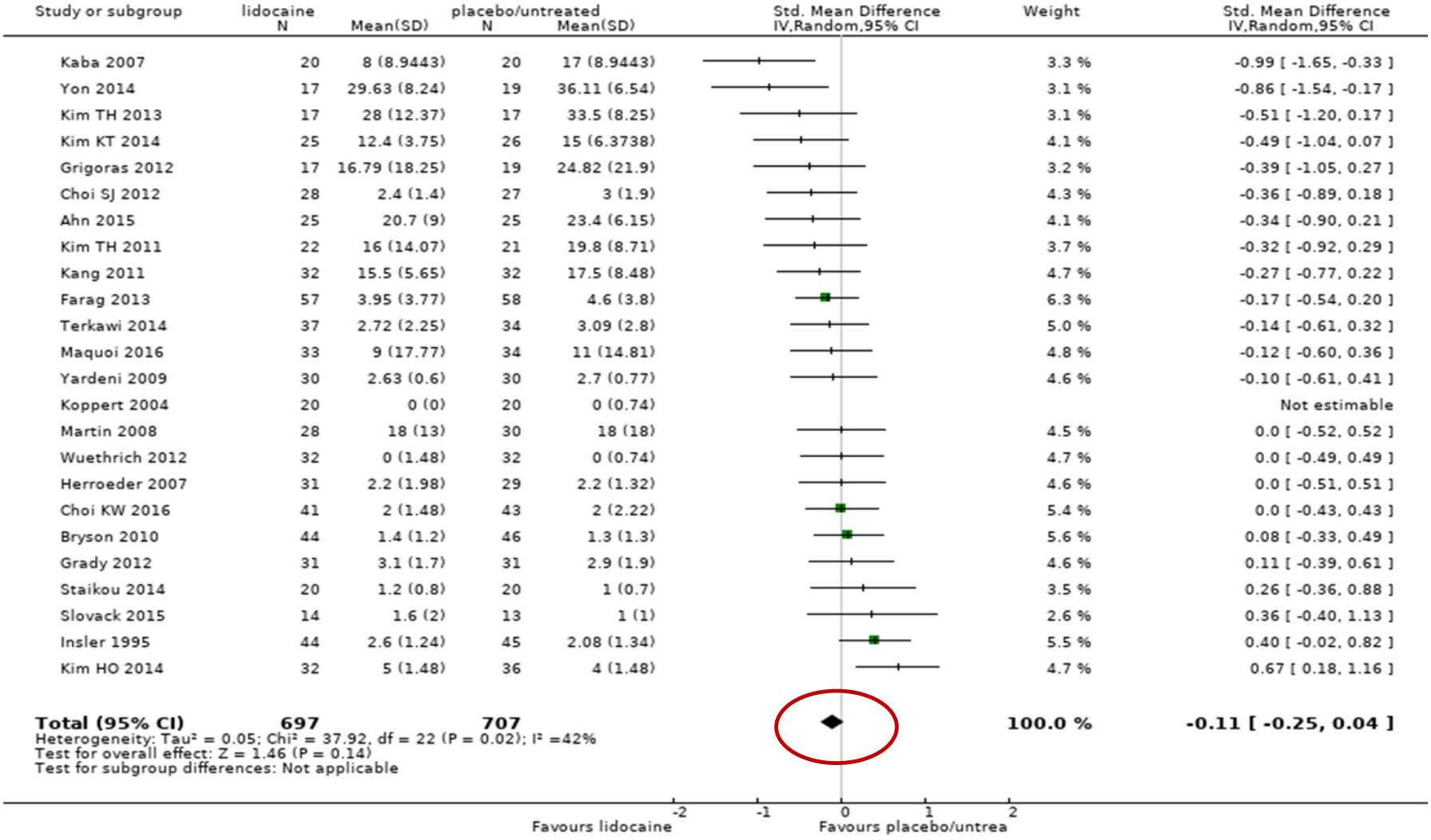

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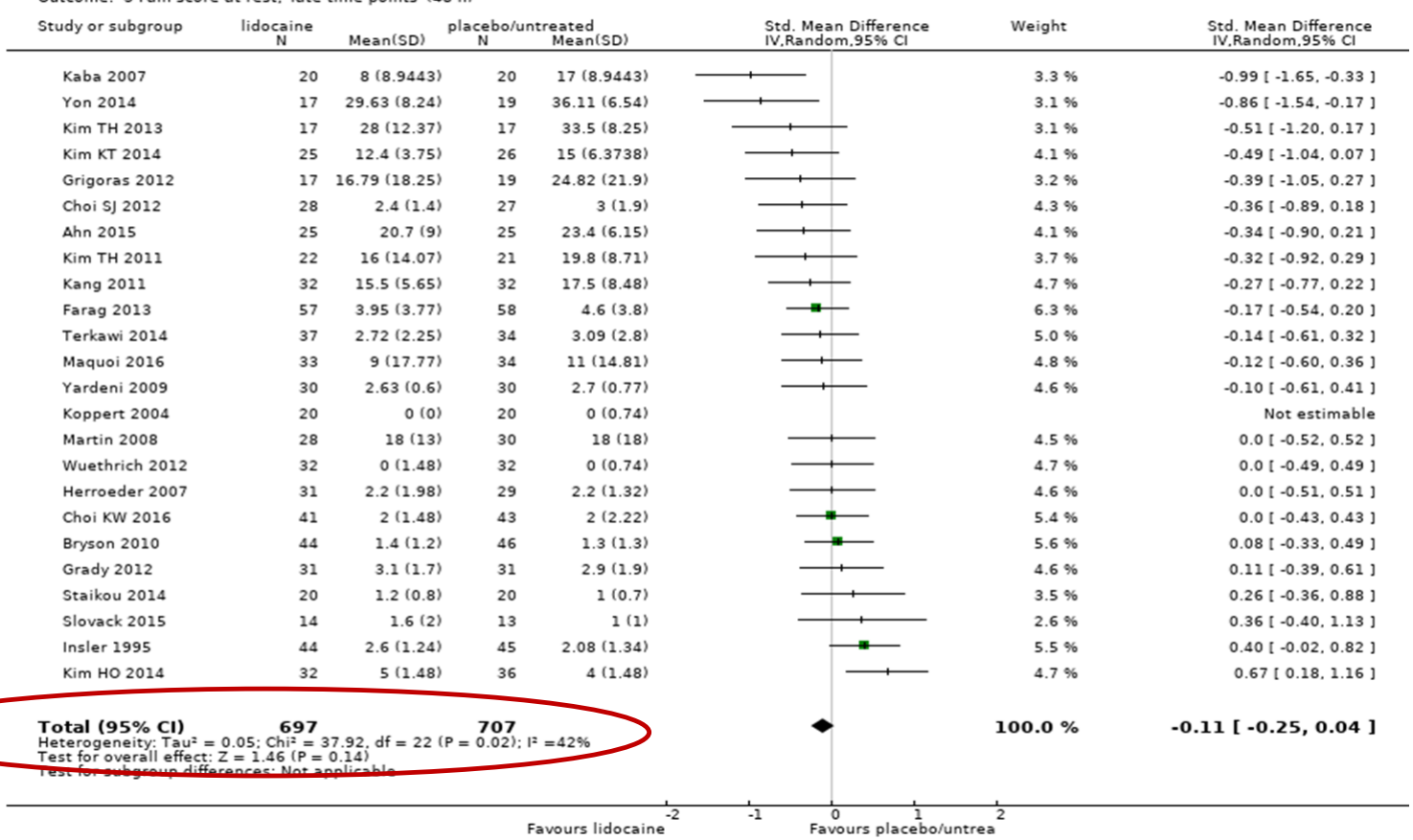


Heterogeneity

- Heterogeneity: *variability in estimates of treatment effects between studies in a meta-analysis*
- Significant heterogeneity suggest that trials are not estimating a single common effect – possibly due to differences in patients, setting, intervention and outcomes
- Can be explored by subgroup and sensitivity analyses
- Usually quantified by I^2 statistic

Clinical and methodological characteristics

- Range of procedures (22 open, 20 laparoscopic abdominal; 26 various)
- People taking opioids or with chronic pain were excluded
- Variation in timing of initiation, bolus size, infusion rates and duration
- Subgroup and sensitivity analyses performed
- ‘Small variance’ trials noted and excluded from analysis

GRADE Quality of Evidence

In the context of a systematic review

- The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct.
- Can be judged '*high*', '*moderate*', '*poor*' or '*very poor*'
- Downgraded for imprecision, bias, heterogeneity etc

Results

- ‘Early’ pain. 29 trials, 1656 patients. Very low certainty evidence.
- SMD (95%CI) -0.50 (-0.72 to -0.28)

Table 9. Sensitivity analyses - with studies with 'suspected variance reporting'

		Without suspicious studies		With suspicious studies	
Outcome	**Statistical method**	**Studies**	**Effect estimate**	**Studies**	**Effect estimate**
Pain score, rest, 'early time points' (1 hr to 4 hrs, PACU)	SMD (IV, Random, 95% CI)	29	−0.50 (−0.72 to −0.28)	37	−0.88 (−1.18 to −0.57)
Pain score, rest, 'intermediate time points' (24 hrs)	SMD (IV, Random, 95% CI)	33	−0.14 (−0.25 to −0.04)	41	−0.29 (−0.44 to −0.15)
Pain score, rest, 'late time points' (48 hrs)	SMD (IV, Random, 95% CI)	24	−0.11 (−0.25 to 0.04)	30	−0.22 (−0.40 to −0.03)
Time to first defaecation/bowel movement (hrs)	MD (IV, Random, 95% CI)	12	−7.92 (−12.71 to −3.13)	14	−7.09 (−10.06 to −4.11)
Time to first flatus (hrs)	MD (IV, Random, 95% CI)	13	−4.09 (−6.30 to −1.87)	16	−5.02 (−7.73 to −2.31)
Time to first bowel sounds (hrs)	MD (IV, Random, 95% CI)	2	−6.08 (−13.77 to 1.60)	4	−4.28 (−10.32 to 1.76)
Postoperative opioid consumption, PACU (MEQ, mg)	MD (IV, Random, 95% CI)	21	−3.10 (−3.87 to −2.32)	25	−3.51 (−4.88 to −2.15)
Postoperative opioid consumption, overall (MEQ, mg)	MD (IV, Random, 95% CI)	40	−4.52 (−6.25 to −2.79)	43	−4.81 (−6.55 to −3.07)

Results

- ‘Early’ pain. 29 trials, 1656 patients. Very low certainty evidence.
- SMD (95%CI) -0.50 (-0.72 to -0.28)
- Corresponds to 0.37 to 2.48 cm on 10cm VAS
- [Benefits of neuraxial *vs.* opioid usually 1-2 cm]
- However, 95% prediction intervals were -1.61 to 0.62
- *‘The range of mean effects to be expected in a future study includes both benefit and harm*’

Results

- Moderate certainty evidence for no effect in ‘intermediate’/’late’ pain
- Suggestion of improved early pain control, reduced morphine consumption, nausea and vomiting and postoperative ileus (low quality evidence).
- *‘The range of mean effects to be expected in a future trial includes both benefit and clinical non-relevance’*

Other meta-analyses

- Marret 2008: 8 RCT, 320 pts: abdominal surgery only [8]
- McCarthy 2010: 16 RCT, 764 pts (abdominal surgery: 12) [15]
- Vigneault 2011: 29 RCT, 1754 pts (abdominal surgery:10) [26]
- Sun 2012: 21 RCT, 1108 pts, abdominal surgery only [15]
- Ventham 2015: Laparoscopic surgery (14 RCT; 3 colorectal) [13]
- Chang 2017: 4 RCT, 167 pts, breast surgery (4 RCTs) [4]

In the pipeline

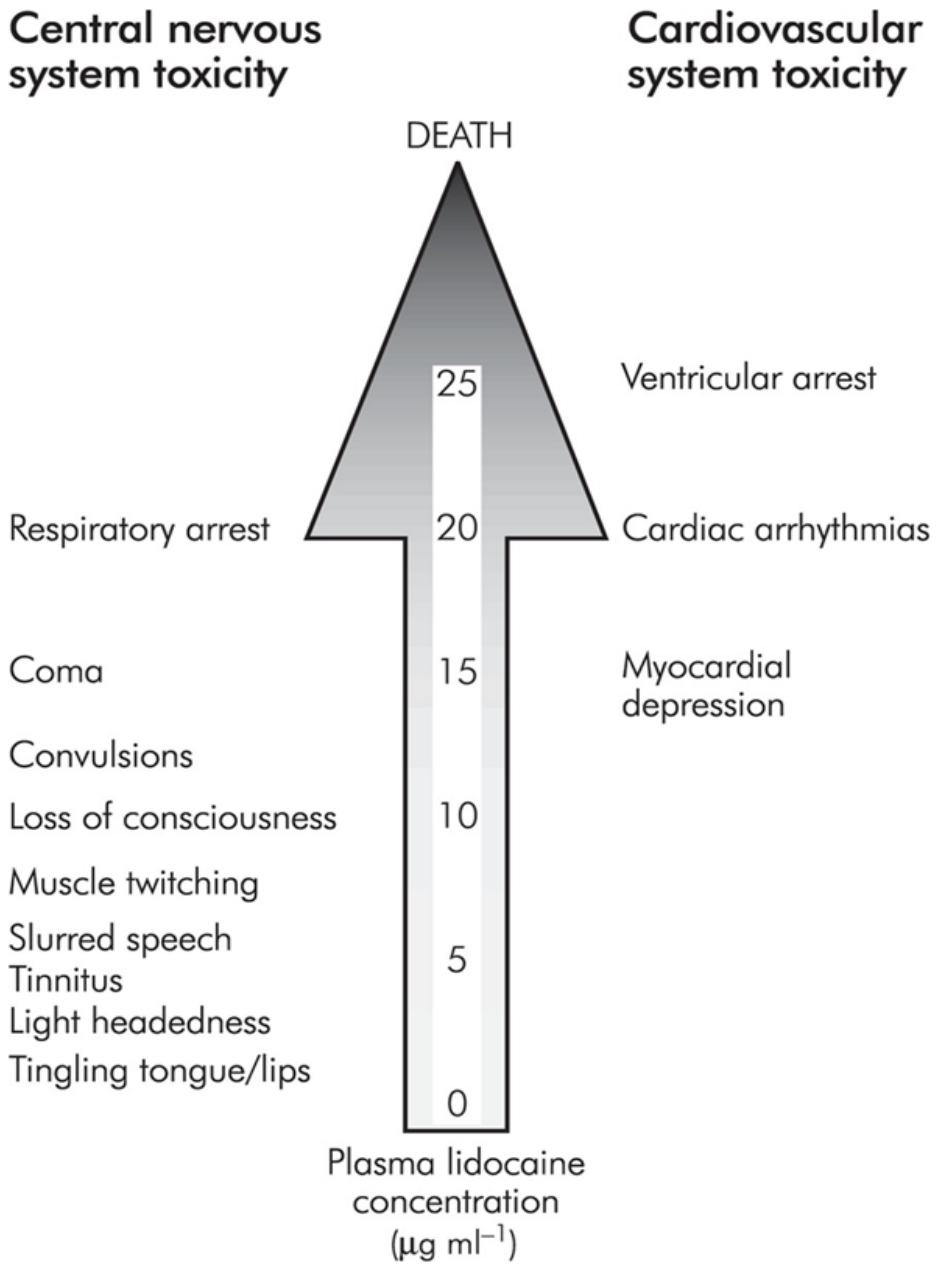
Trial name	Trial registration	Location	Sample size	Study design
ALLEGRO	EudraCT 2017-003835-12	UK	562	1.5 $mg.kg^{-1}$ (ideal body weight) bolus over 20 min followed by 1.5 $mg.kg^{-1}.h^{-1}$ infusion for a minimum of 6 and maximum of 12 h
VAPOR-C	NCT04316013	Australia and international	5736	1.5 $mg.kg^{-1}$ (adjusted body weight) bolus over 20 min then 2 $mg.kg^{-1}.h^{-1}$ for 4 h, then 1.5 $mg.kg^{-1}.h^{-1}$ thereafter until the end of surgery
LOLIPOP	Pending	Australia and international	4600	Intra-operative intravenous lidocaine and postoperative subcutaneous lidocaine for up to 24 h postoperatively (ideal body weight) *(ethics pending)*
PLAN	Pending	Canada and international	1144	1.5 $mg.kg^{-1}$ bolus followed by an infusion of 2 $mg.kg^{-1}.h^{-1}$ for the duration of surgery

2 Is intravenous lidocaine safe?

- 50 of 68 studies gave information on adverse events. Wide variability in data presentation.
- 23 reported no significant adverse events.
- 27 reported typical symptoms of toxicity.

Weibel S et al *Cochrane Database of Systematic Reviews* 2018; Issue 6

Toxicity


Central nervous system toxicity
Cardiovascular system toxicity
DEATH
25
20
15
10
5
0
Ventricular arrest
Cardiac arrhythmias
Myocardial depression
Respiratory arrest
Coma
Convulsions
Loss of consciousness
Muscle twitching
Slurred speech
Tinnitus
Light headedness
Tingling tongue/lips
Plasma lidocaine concentration (μg ml⁻¹)

Local anaesthetic systemic toxicity

- Doctor/staff education
- Systems design
- Equipment, including programming
- Drug preparation
- Patient susceptibility/ selection
- Drug interaction
- Patient monitoring and surveillance

Weinberg G. Perioperative lidocaine infusion: does the risk outweigh the benefit? *Anesth Analg* 2021; 132: 906-9

Safety in practice I

- 2013-7. 544 patients; 394 analysed
- Duration 68.6 (49.4) h
- Infusion rate ‘typically 1 mg. $kg^{-1}.h^{-1}$‘ (0.5-2)
- 56.1% ‘clinically important difference’
- One cardiac arrest due to accidental rapid bolus
- 37 (9.4%) patients had minor side effects

De Oliveira K, Eipe N. Intravenous lidocaine for acute pain: a single-institution retrospective study. *Drugs - Real World Outcomes* 2020; 7: 205-12.

Table 5 List of adverse effects and their associated frequencies

Adverse effect	No. of events
Agitation	4
Blurred vision	1
Cardiac arrest	1
Dizziness	5
Metallic taste	6
Nausea	3
Perioral numbness	3
Rash	1
Somnolence	6
Tachycardia	1
Tinnitus	3
Tremor	3
Visual disturbance	1

De Oliveira K, Eipe N. Intravenous lidocaine for acute pain. *Drugs - Real World Outcomes* 2020; 7: 205-12

Safety in practice II

- 150 women undergoing breast cancer surgery
- 1.5 mg. kg^{-1} then 2 mg. $kg^{-1}.h^{-1}$, 12 h max, on surgical ward

	Lidocaine	Saline
Bradycardia	9%	4%
Hypotension	6.1%	4.3%
MET call	1	2
Infusion stopped	1	2
Catheter site problems	3	0

Toner et al. *Anaesthesia* 2021; 76: 1326-41.

3 What about unlicensed use?

- Prescriber must be satisfied that there is no licensed alternative, and review the evidence base and/or experience to establish safety and efficacy
- Inform patients about treatment, including adverse reactions and record
- Explain reasons if treatment has little evidence or use is innovative
- 'Careful about using medical devices for purposes for which they were not intended'

GMC *Good Practice in Prescribing and Managing Medicines and Devices ,* 2013

DH: *Off-label or unlicensed use of medicines: prescribers' responsibilities*, 2014

But what about……?

- Patients on high dose opioids/substance abuse
- History of chronic pain
- Epidural contraindicated/ refusal
- Epidural inadequate / failure
- Surgical indications – unexpected change of laparoscopic to open procedure
- Extent/ magnitude of surgery (pain) determines success of i.v. lidocaine

Ilford Recorder

'They killed her': Hospital apologises after giving Woodford Green woman 'toxic' overdose of unapproved drug

PUBLISHED: 07:00 17 December 2019 | Imogen Braddick

Yvonne Hewitt and her husband Owen. Picture: Osbornes Law

A hospital has apologised after a Woodford Green woman suffered a catastrophic brain injury when she was accidentally given a "toxic" overdose of an unlicensed and unapproved drug while in intensive care.

What went wrong?

- Gynaecological procedure then urological reconstruction.
- Severe pain postop on ICU
- 2 dose regimens for lidocaine in different tabs on prescribing system
- Nurses unfamiliar and no guidelines to check against
- Arrest attributed to bleeding and/or PE
- Intralipid® not given

What can we do?

A safety guideline

Anaesthesia
Peri-operative medicine, critical care and pain

Association of Anaesthetists

Guidelines | Open Access

The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety

I. Foo, A. J. R. Macfarlane, D. Srivastava, A. Bhaskar, H. Barker, R. Knaggs, N. Eipe, A. F. Smith

First published: 03 November 2020 | https://doi.org/10.1111/anae.15270 | Citations: 6

This article is accompanied by an editorial by Pandit et al. Anaesthesia 2021; **76**: 156–60

Anaesthesia 2021; **76:** 238-50

Recommendations

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4. Explicit consent should be obtained from the patient, with written information as needed
5. Ideal body weight should be used for dosing
6. Minimum body weight 40kg

7. No other concurrent local anaesthetic interventions

- Not within 4 h of any nerve block, and no nerve blocks within 4 h of lidocaine
- No boluses of local anaesthetic into wound/epidural catheters until 4 h after lidocaine infusion finished

  (Infusions may be started after 30 min)
- Wait 2 h after infiltration of laparoscopic port insertion sites

8. Initial dose of no more than 1.5 $mg.kg^{-1}$ over 10 min, given with an anaesthetist present

9. Infusion of 1.5 $mg.\ kg^{-1}.h^{-1}$ thereafter. Change in rate only to be authorised by a consultant

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10. Dedicated, labelled, lockable, tamperproof pump

11. Separate, dedicated cannula with saline infusion and one-way valve

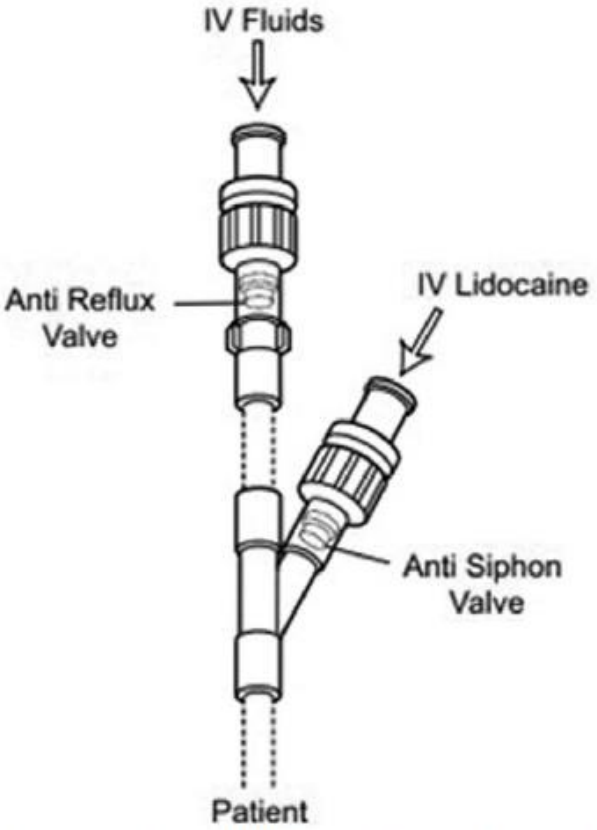

Figure. Ensuring safety of IV lidocaine infusions: the use of IV PCA Y-connector with an integral antisiphon (to prevent free-flow due to gravity) and an antireflux valve (to prevent reflux into main IV line). IV indicates intravenous; PCA, patient-controlled analgesia. Credit from Eipe et al[2]; adapted from the original artwork by Perry Ng, Medical Illustrator, Faculty of Medicine, uOttawa.

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9. Infusion of 1.5 $mg.\ kg^{-1}.h^{-1}$ thereafter. Change in rate only to be authorised by a consultant
10. Dedicated, labelled, lockable, tamperproof pump
11. Separate, dedicated cannula with saline infusion and one-way valve
12. Duration should not exceed 24h
13. Nurse patients in a high dependency area
14. Have lipid emulsion 20% available
15. Remember possibility of lidocaine toxicity

LOLIPOP Lidocaine Infusion Surveillance Tool

Date: ___/___/______

Patient Label

If the Patient answers yes to 2 of the following 5 questions (at the same time point) OR has ANY Toxic signs: STOP THE INFUSION BY REMOVING THE SUBCUTANEOUS CANNULA

Time assessed	Q1 Tingling		Q2 Ringing		Q3 Dizzy		Q4 Visual		Q5 Metallic		Toxic Signs		Time ceased
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
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<u>PATIENT QUESTIONS (Ask every 4 hours)</u>

Q1. Any **Tingling/Pins** and **needles** (especially) around the **Eyes** and **Mouth**?

Q2. Ringing in the **ears**?

Q3. Do you have **Dizziness** that you are finding troubling?

Q4. Obvious **Visual Disturbances (e.g.** seeing **shapes, flashing lights** or **blurriness)?**

Q5. Do you have a **Metallic Taste** in your mouth?

<u>TOXIC SIGNS (At any time)</u>

1. Ongoing **tremor/twitches**
2. **Slurred Speech**
3. Respiratory Rate **<10** (not opioid induced)
4. New Bradycardia **< 50BPM**
5. Tachycardia **> 130BPM**
6. Hypotension: Recurrent fainting or Systolic Blood Pressure **<90**
7. Agitation/Acute Confusion/ **GCS < 14** (excluding sleep)

If infusion stopped for symptoms or signs of lidocaine toxicity, please contact medical staff to review. Monitor for signs of severe local anaesthetic toxicity and treat appropriately (see AAGBI Safety Guideline). In the event of circulatory arrest **<u>INTRALIPID 20%</u>** should be administered intravenously as per below.

INTRALIPID 20% DOSING IN SEVERE TOXICITY			
Patient Weight	kg	Intralipid 20% location on ward:	
Bolus Dose over 1 minute (1.5 ml/kg)	1.5 ml x patient weight	1.5 x	= ml (BOLUS)
Infusion rate after bolus (15 ml/kg/h)	15 ml x patient weight	15 x	= ml/h (INFUSION) (reassess after 5 mins)*
* Refer to attached **AAGBI Safety Guideline** for further dosing details			

Toner et al. A pilot multicentre randomised controlled trial of lidocaine infusion in women undergoing breast cancer surgery. *Anaesthesia* 2021; 76: 1326-41.

Editorial

1 Is i.v. lidocaine supported by a rational mechanism of action?

2 Clinical trial evidence of efficacy

3 Use of unlicensed medications including ‘risk to professional standing of colleagues’

4 Distinctions: drugs/devices, intra- vs. postoperative use

Anaesthesia

Pandit J, McGuire N. Unlicensed intravenous lidocaine for postoperative pain: always a safer 'licence to stop' than to start. *Anaesthesia* 2021; 76: 156- 60.

RCoA statement

Statement on the use of lidocaine infusions to treat postoperative pain

The Royal College of Anaesthetists and its Faculty of Pain Medicine (FPM) are aware of the recent publication in the journal *Anaesthesia* of a "consensus statement" on the use of intravenous lidocaine infusions for the treatment of postoperative pain.

In view of reports of adverse patient safety incidents related to this off-licence use of lidocaine, the College and FPM strongly encourage clinicians wishing to use lidocaine infusions for postoperative pain to read an editorial that accompanied the publication of the consensus statement. It outlines concerns about this use of lidocaine, sets out circumstances under which it might be reasonable to use this technique, and guides clinicians on when stopping lidocaine infusions might be in a patients' best interests.

Professor Ravi Mahajan, President, Royal College of Anaesthetists

Dr John Hughes, Dean, Faculty of Pain Medicine

RCoA
Royal College of Anaesthetists

Responses to editorial

- Lack of knowledge of mechanisms of action is not a problem
- Evidence is not great for many individual interventions: best used as part of a multimodal pain management strategy

Hollman M et al. Intravenous lidocaine: it's all about a risk-benefit analysis. *Anaesthesia* 2021; 76: 717-8.

- Focused on pain (OBAS)
- Misquoted cardiac arrest (Ventham)

Foo I, Eipe N, Smith AF. *Anaesthesia* 2021; 76: 1141-2

Other letters

- Discourages research. No need for upper dose limits. Little difference in plasma levels 1.5 vs. 3 mg. $kg^{-1}.h^{-1}$.

Dubowitz J et al. *Anaesthesia* 2021; 76: 719-20.

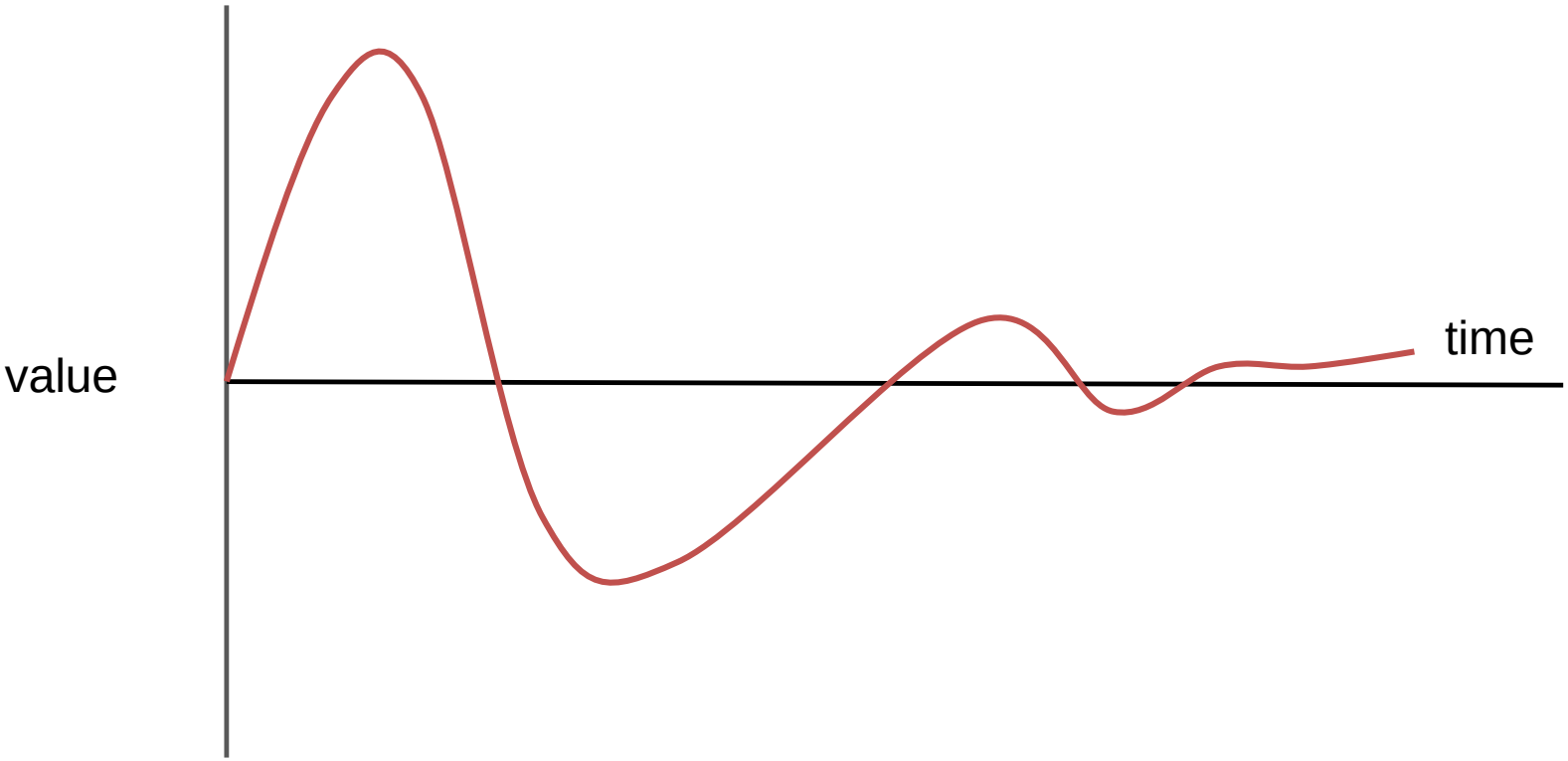
- Recommended dose too low (should have used at least 2 mg. $kg^{-1}.h^{-1}$)

Moyano J et al. *Anaesthesia* 2021; 76: 721.

- 'Knee jerk reaction to a reported death'. 10 mins too slow for initial infusion. 4h limit impractical

McKinney M. *Anaesthesia* 2021; 76: 1140.

The ‘ups and downs’ of new technology



Key messages

- Evidence does not extend to ‘problem’ patients
- Evidence does not always seek all relevant outcomes
- Evidence doesn’t help if things don’t go according to plan
- Our guideline errs on the side of safety: infusion rate and temporal relationship to blocks
- I.v. lidocaine can be used safely and further work is needed to establish its proper place

@ProfAndyS