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Adrenaline with lidocaine for digital nerve blocks (Review)

Prabhakar H, Rath S, Kalaivani M, Bhanderi N

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[Intervention Review]

Adrenaline with lidocaine for digital nerve blocks

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ABSTRACT

Background

Surgery on fingers is a common procedure in emergency and day care surgery. Adrenaline combined with lidocaine can prolong digital nerve block and provide a bloodless operating field. Extended postoperative pain relief can reduce the need for analgesics and can facilitate hand rehabilitation. Conventionally, adrenaline is avoided at anatomical sites with end arteries such as digits, penis and pinna because of concerns about arterial spasm, ischaemia and gangrene distal to the site of drug infiltration.

Objectives

To assess the safety and efficacy of use of adrenaline (any dilution) combined with lidocaine (any dilution) for digital nerve blocks (fingers and toes).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2014), MEDLINE via Ovid SP (1966 to 18 November 2014) and EMBASE via Ovid SP (1980 to 18 November 2014). We also searched specific websites, such as www.indmed.nic.in; www.cochrane-sadcct.org; and http://www. Clinical trials.gov.

Selection criteria

We included randomized controlled trials (RCTs) that compared the use of adrenaline with lidocaine and plain lidocaine in patients undergoing surgery on digits (fingers and toes). Our primary outcomes were duration of anaesthesia, adverse outcomes such as ischaemia distal to the injection site and cost analysis. Our secondary outcomes were duration of postoperative pain relief and reduced bleeding during surgery.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Two review authors independently extracted details of trial methodology and outcome data from reports of all trials considered eligible for inclusion. We performed all analyses on an intention-to-treat basis. We used a fixed-effect model when no evidence of significant heterogeneity between studies was found and a random-effects model when heterogeneity was likely.

Main results

We included four RCTs with 167 participants. Risk of bias of the included studies was high, as none of them reported method of randomization, allocation concealment or blinding. Only one trial mentioned our primary outcome of duration of anaesthesia. The mean difference in duration of anaesthesia with use of adrenaline with lidocaine was 3.20 hours (95% confidence interval (CI) 2.48 to 3.92 hours; one RCT, 20 participants; low-quality evidence). No trial reported adverse events such as ischaemia distal to the injection site, and no

trial reported cost analysis. One trial mentioned the secondary outcome of duration of postoperative pain relief, but available data were insufficient for analysis of the findings. Two trials reported the secondary outcome of reduced bleeding during surgery.

Bleeding during surgery was observed in nine out of 52 participants as compared with 25 out of 51 participants in the adrenaline with lidocaine and plain lidocaine groups, respectively. The risk ratio for bleeding in the adrenaline with lidocaine group was 0.35 (95% CI 0.19 to 0.65; two RCTs, 103 participants; low-quality evidence).

Authors' conclusions

From the limited data available, evidence is insufficient to recommend use or avoidance of adrenaline in digital nerve blocks. The evidence provided in this review indicates that addition of adrenaline to lidocaine may prolong the duration of anaesthesia and reduce the risk of bleeding during surgery, although the quality of the evidence is low. We have identified the need for researchers to conduct large trials that focus on other important outcomes such as adverse events, cost analysis and duration of postoperative pain relief.

PLAIN LANGUAGE SUMMARY

Use of adrenaline with lidocaine for surgery on fingers and toes

Review question: We reviewed the evidence on the use of adrenaline with lidocaine for surgery on fingers and toes.

Background: Surgery on fingers and toes is commonly performed on individuals under local anaesthesia. Adrenaline is added to a local anaesthetic to prolong its effect. However, caution is recommended when adrenaline is used in body parts with end arteries, that is, arteries that are the only blood supply of that particular organ, for example, fingers and toes. Adrenaline may constrict the arteries and reduce blood supply to those organs, resulting in complications. We wanted to discover whether any evidence is available to support this conventional teaching.

Study characteristics: Evidence is current to November 2014. We included studies in children (aged older than 28 days and younger than 18 years) and adult patients (aged 18 years or older) of either gender undergoing surgery on digits (fingers and toes) under nerve blocks using adrenaline with lidocaine.

Key results: We found four eligible studies with 167 participants.

One small study reported the duration of anaesthesia and found that adrenaline prolonged the duration of anaesthesia, but the quality of the evidence was low.

No study reported on adverse events such as ischaemia distal to the injection site or cost analysis with use of adrenaline with lidocaine.

Duration of postoperative pain relief was reported by one study, but available data were insufficient for analysis of the findings.

Two studies reported reduced bleeding during surgery with use of adrenaline with lidocaine. In the light of our results, we would expect that 17.2 out of 100 patients who received adrenaline with lidocaine (between 8.7 and 29.8 patients) would have bleeding during surgery compared with 49 patients who would have received plain lidocaine; however, the quality of the evidence was low, and further research is very likely to impact our confidence in this estimate.

Quality of evidence

The quality of evidence is low for both duration of anaesthesia and bleeding during surgery with use of adrenaline with lidocaine. Further research is needed to prove the benefits of adding adrenaline to lidocaine.

Summary of findings 1. Lidocaine vs lidocaine with adrenaline for digital nerve blocks

Lidocaine vs lidocaine with adrenaline for digital nerve blocks

Patient or population: patients with digital nerve blocks
Settings: hospital
Intervention: lidocaine vs lidocaine with adrenaline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lidocaine vs lidocaine with adrenaline				
Duration of anaesthesia Time period[a]		Mean duration of anaesthesia in the intervention groups was **3.2 higher** (2.48 to 3.92 higher)		20 (1 study)	⊕⊕⊝⊝ **Low** [b,c]	
Adverse outcomes						No data were available
Cost analysis						No data were available
Duration of postoperative pain relief						No data were available
Bleeding during surgery Subjective assessment[d]	**Study population**		**RR 0.35** (0.19 to 0.65)	103 (2 studies)	⊕⊕⊝⊝ **Low** [e,f]	
	490 per 1000	**172 per 1000** (93 to 319)				
	Moderate					
	459 per 1000	**161 per 1000** (87 to 298)				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Duration in hours.
[b]Method of randomization and blinding not mentioned.
[c]Single trial.
[d]Assessed by operating surgeon as increased or decreased bleeding.
[e]Methods of randomization and allocation not clear in the study by Andrades 2003. Selection and detection bias noted in the study by Wilhelmi 2001.
[f]One trial by Andrades 2003 shows imprecision, but the one by Wilhelmi 2001 shows appreciable benefit.

BACKGROUND

Surgery on fingers is a common procedure in emergency and day care surgery (Angermann 1993). Adrenaline (any dilution) combined with lidocaine can prolong digital nerve block and provide a bloodless operating field. Extended postoperative pain relief can reduce the need for analgesics and can facilitate hand rehabilitation. Conventionally, adrenaline was avoided at anatomical sites with end arteries such as digits, penis and pinna due to concerns about arterial spasm, ischaemia and gangrene distal to the site of drug infiltration (Wilhelmi 2001). End arteries, which are also known as *terminal arteries,* serve as the only supply of blood to a particular body part. Evidence for the safety of adrenaline and its benefits is limited, hence the need for this review.

Description of the condition

Finger injuries commonly result from industrial, domiciliary and road traffic accidents (Angermann 1993). Most of these injuries are treated in emergency departments or in day care centres. Digital nerve block with lidocaine is a convenient and successful technique with low complication rates and high patient acceptance (Thomson 2006). The only limitation of this approach is that the duration of nerve block with lidocaine is short, and additional administration may be required during surgery.

Description of the intervention

Adding adrenaline to lidocaine significantly increases the duration of anaesthesia (Sonohata 2012) because adrenaline causes constriction of the blood vessels and thereby delays absorption of the drug from the site of administration.

How the intervention might work

Adrenaline causes vasoconstriction of surrounding vessels and restricts absorption of lidocaine, thereby increasing the duration of anaesthesia (Wilhelmi 1998). The vasoconstrictive effect provides a bloodless operating field, which is an added benefit (Lalonde 2005; Wilhelmi 2001).

Why it is important to do this review

Combining adrenaline with lidocaine for regional or local nerve blocks significantly increases the duration of anaesthesia. When adrenaline is used as local infiltration anaesthesia, its vasoconstrictive effect is an added benefit, as this provides a bloodless operating field. Historically, adrenaline was not used conventionally for digital nerve block because of the risk of digital ischaemia from vasoconstriction of the end arteries (Wilhelmi 2001). However, the evidence on the safety of modern commercial adrenaline preparations for digital nerve block has evolved over time (Chapeskie 2016; Ilicki 2015). This systematic review gathered available evidence for the safety of use of adrenaline (any dilutions) with lidocaine (any dilutions) for digital nerve blocks (fingers and toes) and compared the duration of this combination anaesthesia with that of lidocaine alone.

OBJECTIVES

To assess the safety and efficacy of use of adrenaline (any dilution) combined with lidocaine (any dilution) for digital nerve blocks (fingers and toes).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared the use of adrenaline with lidocaine versus plain lidocaine in participants undergoing surgery for digits (fingers and toes). We excluded quasi-randomized, cluster-randomized and cross-over trials.

We excluded studies in which any other adjuvant was used along with lidocaine in the same participant. We also excluded studies in which any other anaesthetic technique was used along with lidocaine in the same participant.

Types of participants

We included in our review all adult (age ≥ 18 years) and paediatric (age < 18 years) participants of either gender undergoing surgery on digits (fingers and toes) under nerve blocks using adrenaline with lidocaine.

We excluded neonates from our review.

Types of interventions

Our experimental group included participants receiving peripheral nerve blocks with a lidocaine and adrenaline mixture.

Our control group included participants receiving peripheral nerve blocks with lidocaine only.

Types of outcome measures

Primary outcomes

- Duration of anaesthesia reported in minutes/hours.
- Adverse outcome such as ischaemia distal to the injection site reported as a dichotomous outcome.
- Cost analysis.

Secondary outcomes

- Duration of postoperative pain relief reported in minutes/hours.
- Reduced bleeding during surgery (reported as a dichotomous outcome, yes or no/increased or decreased bleeding), as suggested by the operating surgeon.

Outcomes were not included in the study eligibility assessment, so that studies meeting participant, intervention and comparison criteria were included in the review even if they reported no relevant outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2014; see Appendix 1), MEDLINE via Ovid SP (1966 to 18 November 2014; see Appendix 2) and EMBASE via Ovid SP (1980 to 18 November 2014; see Appendix 3). The MEDLINE and EMBASE search strategy was combined with the highly sensitive Cochrane search filter in identifying RCTs (Lefebvre 2011).

We applied no language restrictions.

Searching other resources

We used the terms "adrenaline with lidocaine", "digital nerve blocks", "lidocaine for nerve blocks" and "adrenaline and lidocaine" to search for relevant trials on specific websites such as:

- www.indmed.nic.in;
- www.cochrane-sadcct.org; and
- http://www. Clinical trials.gov.

Data collection and analysis

Selection of studies

Using studies identified by the above searches, we screened all titles and abstracts for eligibility. Two review authors (SR and NB) independently performed this screening. We obtained and assessed for relevance the full articles of all potentially eligible RCTs based on the preplanned checklist. Each review author documented the reason for exclusion of each excluded trial. We resolved disagreements between the two review authors by discussion and consensus. We compiled a list of all eligible trials.

Data extraction and management

Two review authors (NB and HP) independently extracted data and assessed trial quality using a standardized form (see Appendix 4). For all additional information required, HP contacted the first author of the relevant trial. All studies were published in the English language and did not require translation.

We contacted the study authors mainly to confirm the complete methodology of their study and results. We did not extract numerical data from graphs or figures.

Assessment of risk of bias in included studies

Two review authors (NB and HP) independently assessed the methodological quality of eligible trials. We performed this assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the quality of these studies on the basis of the following quality domains.

- Random sequence generation.
- Allocation concealment.
- Blinding and outcome.
- Incomplete outcome reporting.
- Publication and any other bias.

We considered a trial as having low risk of bias when all domains were assessed as adequate. We considered a trial as having high risk of bias when one or more domains were assessed as inadequate or unclear.

We included a 'Risk of bias' table as part of the Characteristics of included studies table and a 'Risk of bias summary' figure, which detailed all judgements made for all studies included in the review.

Measures of treatment effect

We undertook the analysis using RevMan 5.3 software. We used risk ratio (RR) to measure treatment effect for proportions (dichotomous outcomes) among primary and secondary outcomes and adverse effects. We converted continuous data to the mean difference (MD) using the inverse variance method, and we calculated an overall MD. As an estimate of the statistical significance of a difference between experimental and control interventions, we calculated RRs and MDs between groups along with 95% confidence intervals (CIs). We assumed a statistically significant difference between intervention and control groups when the 95% CI did not include the value of no differential effect.

Unit of analysis issues

We included in our review only RCTs with a parallel-group design. The nature of the intervention suggests that unit of analysis issues, such as those associated with cluster randomization, were unlikely to arise.

Dealing with missing data

We planned to perform quantitative analysis on an intention-to-treat (ITT) basis and to contact study authors to obtain missing data. We planned to analyse missing data, if any, by imputation using best-case and worst-case scenario methods. If we find insufficient data, we will consider the potential impact of the missing data in our interpretation of results.

Assessment of heterogeneity

We performed meta-analysis of data from only two included studies (Andrades 2003; Wilhelmi 2001). We had planned to use the Q statistic to test statistical heterogeneity between trials with $P \leq 0.05$ considered as indicating significant heterogeneity; we used the I^2 statistic to assess the magnitude of heterogeneity (Higgins 2002). We considered $I^2 > 50\%$ to indicate that a meta-analysis was not appropriate, and we used a random-effects model for analysis if the I^2 statistic was between 30% and 50%.

Assessment of reporting biases

We planned to assess publication bias and small-study effect in a qualitative manner by using a funnel plot. We included four studies in this review; therefore we were unable to test for funnel plot asymmetry, which requires inclusion of more than 10 studies in the meta-analysis.

Data synthesis

We quantitatively reviewed the included data and combined data by intervention, outcome and population using the statistical software of The Cochrane Collaboration (RevMan 5.3). We synthesized the data only in the absence of important clinical or statistical heterogeneity, and we expressed pooled estimates of the mean difference (MD) for continuous variables and of the risk ratio (RR) for proportions, as described above. We used the fixed-effect model, as we noted no evidence of significant heterogeneity between studies (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

Where appropriate, when clinical or statistical ($I^2 > 40\%$) heterogeneity was obvious, we planned to consider subgroup analysis based on different doses of lidocaine, different concentrations of adrenaline, different surgical sites (fingers and toes) and differences in participant gender and age (paediatric or adult participants), as well as different techniques used for digital nerve block, such as webspace block, transthecal block and three- and four-sided digital block.

Sensitivity analysis

We planned to perform sensitivity analysis to explore the consistency of effect size measures in trials with low risk of bias versus high risk of bias, and to investigate the impact of missing data using the imputation method described above.

Summary of findings and assessment of the certainty of the evidence

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes (duration of anaesthesia and reduced bleeding during surgery) in our review and constructed a 'Summary of findings' (SoF) table using GRADE software. We did not construct an SoF table for other outcomes such as ischaemia distal to the injected site, nor for cost analysis or assessment of duration of postoperative pain relief. The GRADE approach involves appraising the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence is determined by consideration of within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

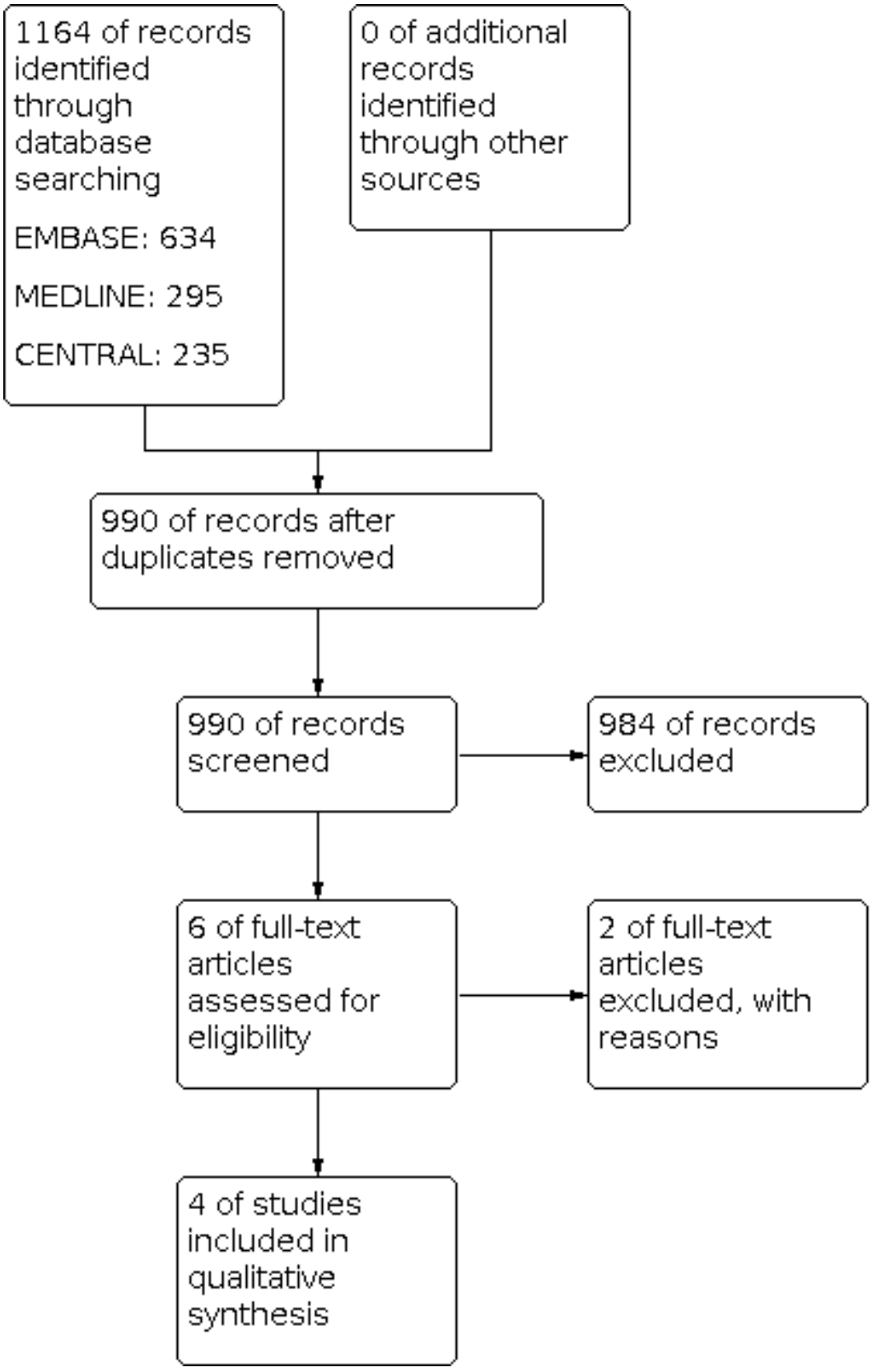
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We identified 1164 records based on our searches of three databases - MEDLINE, EMBASE and CENTRAL - and none from other websites. After duplicate removal, we screened 990 records, of which 984 were removed. Of the six studies assessed for eligibility, we excluded two and included only four studies for qualitative synthesis. See Figure 1

Figure 1. Study flow diagram.



Included studies

We included four studies in our review (Altinyazar 2010; Andrades 2003; Sönmez 2008; Wilhelmi 2001). Altinyazar 2010 enrolled 44 participants; Andrades 2003 enrolled 43 participants; Sönmez 2008 enrolled 20 participants; and Wilhelmi 2001 enrolled 60 participants. All studies were single-centre trials with the same intervention and comparator groups. None of the studies reported the source of funding. All studies were of parallel design, and all except Wilhelmi 2001 used 1:100,000 concentrations of adrenaline with lidocaine; Wilhelmi 2001 used adrenaline in the concentration of 1: 200,000. Only one study (Sönmez 2008) reported our primary outcome of duration of anaesthesia. One study reported duration of postoperative pain relief (Andrades 2003), and two studies reported bleeding during surgery (Andrades 2003; Wilhelmi 2001).

Excluded studies

We excluded two studies for the reasons detailed in the Characteristics of excluded studies table. These two studies (Alhelail 2009; Thomson 2006) were conducted on volunteers, not on patients.

Risk of bias in included studies

We assessed risk of bias of included studies using the 'Risk of bias' tool developed by The Cochrane Collaboration (Higgins 2011). The 'Risk of bias' tool invites judgements on five items for each trial (selection bias, performance bias, detection bias, attrition bias, reporting bias). All review authors independently assessed risk of bias for each study. We resolved disagreements by discussion. We have shown the characteristics of included studies used for our assessment of risk of bias in Figure 2 and Figure 3. We found no study to be of high methodological quality.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

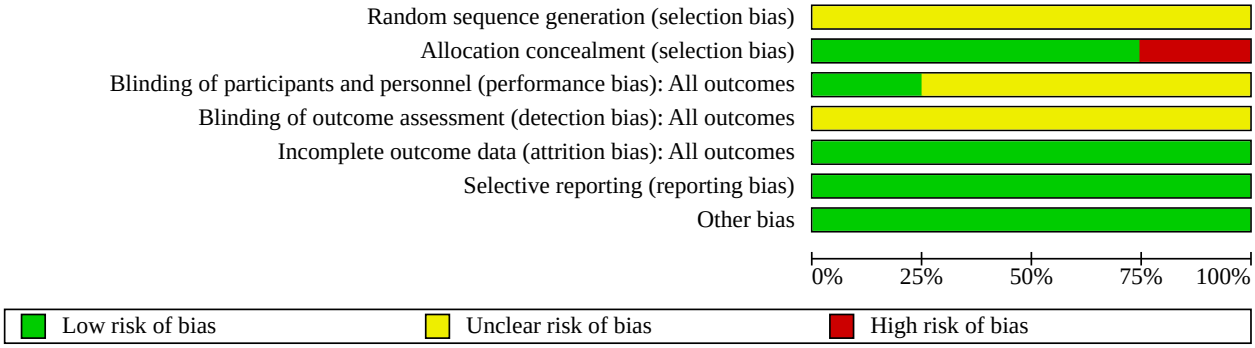
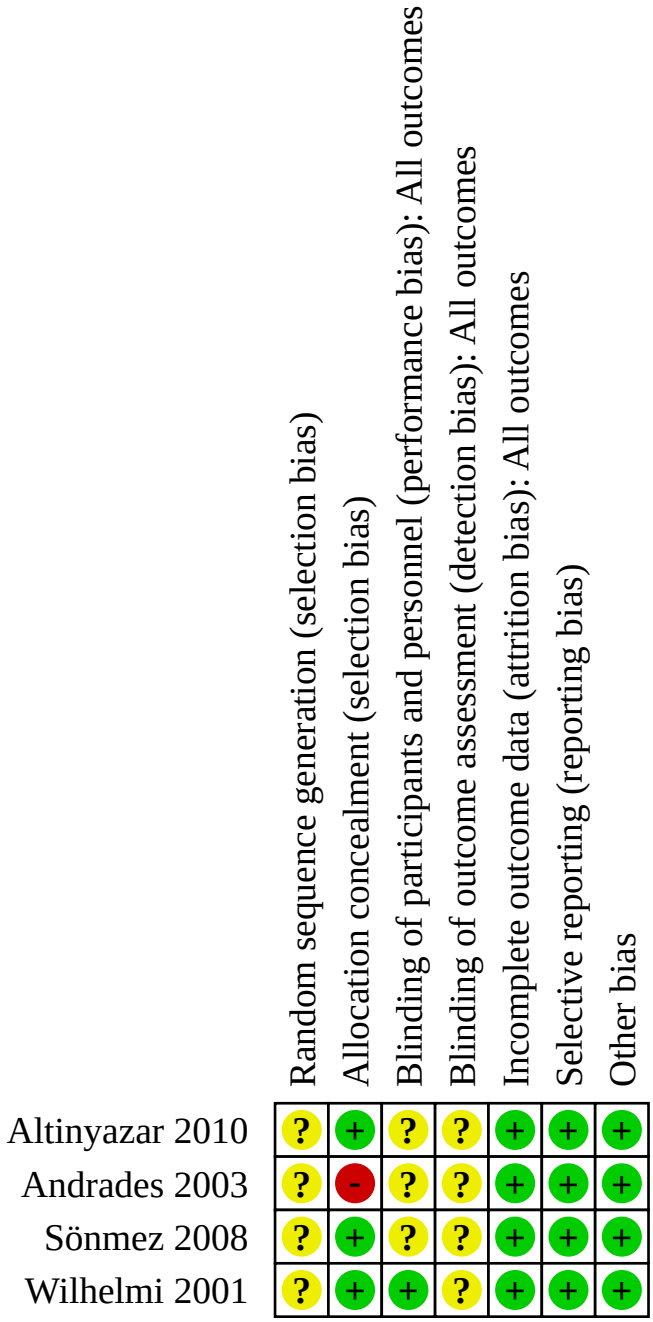


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Of the four included studies, only three (Altinyazar 2010; Sönmez 2008; Wilhelmi 2001) reported allocation concealment. The remaining study (Andrades 2003) did not describe allocation concealment.

Blinding

Of the four included studies, only one (Wilhelmi 2001) reported blinding of participants and personnel; no study reported blinding of the outcome assessor.

Incomplete outcome data

All four included studies reported data on all participants enrolled in the study.

Selective reporting

We found that studies reported all planned outcomes mentioned in their methodology.

Other potential sources of bias

We found no other potential source of bias in any of the included studies.

Effects of interventions

See: **Summary of findings 1** Lidocaine vs lidocaine with adrenaline for digital nerve blocks

Primary outcomes

Duration of anaesthesia

Only one study (Sönmez 2008) enrolling 20 participants (11.9% of the total participants in this review) reported this outcome. The mean difference observed with use of adrenaline with lidocaine was reported in hours (MD 3.20, 95% CI 2.48 to 3.92).

Adverse events

No study reported this outcome.

Cost analysis

No study reported this outcome.

Secondary outcomes

Duration of postoperative pain relief

One study enrolling 43 participants reported duration of postoperative pain relief (25.7% of total participants in this review) (Andrades 2003). Study authors reported that average duration of postoperative pain relief was 4.2 hours and 2.4 hours in the adrenaline with lidocaine and plain lidocaine groups, respectively. The report provided no additional data that could be used to analyse study findings on postoperative pain relief.

Reduced bleeding during surgery

Two studies (Andrades 2003; Wilhelmi 2001) enrolling 43 and 60 participants, respectively, reported reduction in bleeding during surgery (61.7% of total participants in this review). Findings of these trials suggest that the risk ratio of bleeding in the adrenaline with lidocaine group was 0.35 (95% CI 0.19 to 0.65) (Analysis 1.1).

DISCUSSION

This review concerns available randomized evidence for the use of adrenaline with lidocaine for digital nerve blocks. We planned to include randomized clinical trials (RCTs) in this review. However, the few RCTs included in this review were of poor methodological quality. We planned to collect data on clinically relevant outcomes such as duration of anaesthesia, adverse events, cost analysis, duration of postoperative pain relief and reduction in bleeding during surgery. We were able to collect limited data on duration of anaesthesia and reduction in bleeding during surgery. We believe that a comprehensive search was conducted and that missing trials are unlikely.

Summary of main results

One study (Sönmez 2008) reported one of our primary outcomes. Only two studies (Andrades 2003; Wilhelmi 2001) reported our secondary outcomes. Our analysis suggests that evidence for only one of our secondary outcomes of reduced bleeding during surgery is limited. We found that the addition of adrenaline to lidocaine is beneficial in prolonging the duration of anaesthesia and in reducing risk of bleeding during the intraoperative period in patients undergoing surgery on fingers.

Overall completeness and applicability of evidence

Evidence was derived from a limited number of studies (four). We were unable to retrieve sufficient data on any of the clinically useful outcomes such as duration of anaesthesia, adverse events, cost analysis and duration of postoperative pain relief. The evidence produced by this review should therefore be interpreted with caution, with awareness that it is only the reduction in intraoperative bleeding that may be achieved more effectively with the use of adrenaline with lidocaine.

Quality of the evidence

We selected RCTs for our review and noted that all included studies (four) did not report complete details of randomization, allocation concealment and blinding. The overall methodological quality of the four included studies cannot be considered good. The included studies had a homogenous population, and only 13% heterogeneity was noted. For the outcomes of duration of anaesthesia and reduction in bleeding during surgery, the quality of evidence was low, as suggested by the Summary of findings 1.

Potential biases in the review process

In an attempt to minimize bias, we followed the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions*. Two review authors independently assessed eligibility for inclusion and exclusion and risk of bias of individual studies.

Agreements and disagreements with other studies or reviews

We are unaware of any previous review that compared adrenaline with lidocaine versus plain lidocaine for digital nerve blocks.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of our Cochrane review are not robust enough for review authors recommend or refute the use of adrenaline with lidocaine during surgeries on toes and fingers.

Implications for research

Randomized controlled trials with uniform and standard methodology are needed. Proper methods of randomization and blinding should be followed. Use of a standard dose of adrenaline with lidocaine should be an important consideration in the RCT. It is imperative that researchers consider patient-related outcomes such as duration of anaesthesia, adverse events, cost analysis, duration of postoperative pain relief and reduced bleeding during

surgery when designing the study. The RCTs should be adequately powered. A multi-centre trial involving centres in different parts of the world would probably be useful.

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Sonohata M, Nagamine S, Maeda K, Ogawa K, Ishii H, Tsunoda K, et al. Subcutaneous single injection digital block with epinephrine. *Anesthesiology Research and Practice* 2012;**2012**:487-650. [PMID: 21822431]

Wilhelmi 1998

Wilhelmi BJ, Blackwell SJ, Miller J, Mancoll JS, Phillips LG. Epinephrine in digital blocks: revisited. *Annals of Plastic Surgery* 1998;**41**(4):410-4. [PMID: 9788222]

References to other published versions of this review

Prabhakar 2013

Prabhakar H, Rath S, Kalaivani M. Adrenaline with lidocaine for digital nerve blocks. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No: CD010645. [DOI: 10.1002/14651858.CD010645]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altinyazar 2010

Study characteristics	
Methods	RCT, single centre, Turkey Study period: not mentioned Funding source: not mentioned Declaration of interest: not mentioned
Participants	Total: 44 (22 participants (8 female, 14 male) in the control group and 22 (13 female, 9 male) in the lidocaine-epinephrine group) Inclusion: patients with ingrown toe nail Exclusion: patients with peripheral vascular disease, diabetes mellitus, cardiac problems and any evidence of digital infection, gangrene or bone fracture
Interventions	Control: 1 mL of 2% lidocaine Intervention: 1 mL of 2% lidocaine with epinephrine (1:100,000)
Outcomes	Postoperative pain
Notes	Study author contacted. No response

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization not mentioned Study authors contacted
Allocation concealment (selection bias)	Low risk	'Codes in sealed envelopes'. Allocation concealment probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants reported
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methodology reported

Altinyazar 2010 *(Continued)*

Other bias	Low risk	Nothing suggestive

Andrades 2003

Study characteristics	
Methods	RCT, single centre, Chile Study period: October 2001 to May 2002 Funding source: not mentioned Declaration of interest: not mentioned
Participants	Total: 43 Inclusion: patients with lesions In fingers or toes seen in 1 shift in Emergency unit Exclusion: not mentioned
Interventions	Control: 2% lidocaine, 1.5 mL in each digital nerve Intervention: 2% lidocaine with epinephrine (1:100,000), 1.5 mL in each digital nerve
Outcomes	Duration of analgesia Bleeding
Notes	Visual analogue scale used for assessment of pain (1 = no pain, 10 = maximum pain) Bleeding assessed by need for tourniquet or other maneuvers for bleeding control such as compression or deep sutures Study authors contacted for details. No response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Exact method not mentioned Study authors contacted for details. No response
Allocation concealment (selection bias)	High risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Attending physician blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants reported

Andrades 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methodology reported
Other bias	Low risk	Nothing suggestive

Sönmez 2008

Study characteristics	
Methods	RCT, single centre, Turkey Study period: October 2006 to February 2007 Funding source: not mentioned Declaration of interest: not mentioned
Participants	Total: 20 participants Inclusion: patients undergoing finger surgery Exclusion: Patients with known peripheral vascular disease, diabetes mellitus, Raynaud's syndrome, systemic sclerosis, CREST syndrome or any vasospastic disorder were not included in the study. Also, patients suffering from traumatic digital injuries were not included
Interventions	Control: plain 2% lidocaine group (n = 10) Intervention: 2% lidocaine with epinephrine (1:100,000) (n = 10)
Outcomes	Time to regain full sensation (duration of anaesthesia)
Notes	Study authors contacted for details. No response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Exact method not mentioned
Allocation concealment (selection bias)	Low risk	'Codes in sealed envelopes'; allocation concealment probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants reported

Sönmez 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methodology reported
Other bias	Low risk	Nothing suggestive

Wilhelmi 2001

Study characteristics		
Methods	RCT, single centre, Texas (USA) Study period: not mentioned Funding source: not mentioned Declaration of interest: not mentioned	
Participants	Total: 60 participants Inclusion: patients with post-traumatic injuries or elective conditions of fingers Exclusion: not mentioned	
Interventions	Control: plain lidocaine group (n = 29) Intervention: lidocaine (1%) with epinephrine (1:200,000) group (n = 31)	
Outcomes	Duration of action Need for tourniquet (increased bleeding)	
Notes	Study authors contacted for details. No response	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Statistician randomized, but no mention how?
Allocation concealment (selection bias)	Low risk	'Vials placed in emergency room, Pyxis drug dispenser, and administered in numerical order as ascribed by the statistician'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Patients and physicians were blinded'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants reported

Wilhelmi 2001 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methodology reported
Other bias	Low risk	Nothing suggestive

RCT = randomized controlled trial.
USA = United States of America.
CREST = calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alhelail 2009	No control group. Study carried out on volunteers
Thomson 2006	Study carried out on healthy volunteers not undergoing surgery

DATA AND ANALYSES

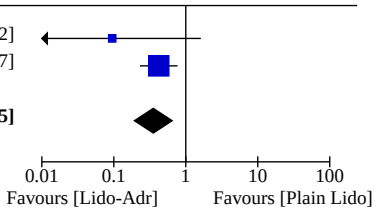
Comparison 1. Lidocaine vs lidocaine with adrenaline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Bleeding during surgery	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.19, 0.65]

Analysis 1.1. Comparison 1: Lidocaine vs lidocaine with adrenaline, Outcome 1: Bleeding during surgery

Study or Subgroup	Lidocaine plus adrenaline Events	Total	Lidocaine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andrades 2003	0	21	5	22	20.6%	0.10 [0.01 , 1.62]
Wilhelmi 2001	9	31	20	29	79.4%	0.42 [0.23 , 0.77]
Total (95% CI)		**52**		**51**	**100.0%**	**0.35 [0.19 , 0.65]**
Total events:	9		25			

Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 3.38 (P = 0.0007)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Lidocaine] explode all trees
#2 MeSH descriptor: [Epinephrine] explode all trees
#3 #1 and #2
#4 ((adrenalin* or epinephrine*) and lidocain*)

#5 #3 or #4
#6 MeSH descriptor: [Nerve Block] explode all trees
#7 ((nerve block* or injur*) near (digit* or finger*))
#8 #6 or #7
#9 #5 and #8

Appendix 2. Ovid MEDLINE search strategy

1. (exp Epinephrine/ and exp Lidocaine/) or ((adrenalin* or epinephrine*) and lidocain*).af.
2. exp Nerve Block/ or ((nerve block* or injur*) adj5 (digit* or finger*)).mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 3. EMBASE (Ovid SP) search strategy

1. (exp adrenalin/ and exp lidocaine/) or exp adrenalin plus lidocaine/ or ((adrenalin* or epinephrine*) and lidocain*).af.
2. exp nerve block/ or ((nerve block* or injur*) adj5 (digit* or finger*)).mp.
3. 1 and 2
4. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 4. Data extraction form

Review title or ID

Study ID *(surname of first author and year first full report of study was published (e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1. General information

Date form completed *(dd/mm/yyyy)*

Name/ID of person extracting data

Report title

(title of paper/abstract/report from which data are extracted)

Report ID

(ID for this paper/abstract/report)

Reference details

Report author contact details

Publication type

(e.g. full report, abstract, letter)

Study funding sources

(including role of funders)

Possible conflicts of interest

(for study authors)

Notes:

2. Study eligibility

Study characteristics	Eligibility criteria *(insert eligibility criteria for each characteristic as defined in the Protocol)*	Yes	No	Unclear	Location in text *(pg & ¶/fig/table)*

(Continued)

Type of study	Randomized controlled trial	
Participants		
Types of interventions		
Types of outcome measures		
INCLUDE	**EXCLUDE**	
Reason for exclusion		
Notes:		

DO NOT PROCEED IF STUDY WAS EXCLUDED FROM THE REVIEW.

3. Population and setting

	Description *(include comparative information for each group (i.e. intervention and controls) if available)*	**Location in text** *(pg & ¶/fig/table)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Notes:		

4. Methods

	Descriptions as stated in report/paper	**Location in text**

(Continued)

	(pg & ¶/fig/table)
Aim of study	
Design *(e.g. RCT)*	
Unit of allocation *(by individuals, clusters/groups or body parts)*	
Start date	
End date	
Total study duration	
Ethical approval needed/obtained for study	Yes No Unclear
Notes:	

5. Risk of bias assessment

See Chapter 8 of the Cochrane Handbook for Systematic Reviews of Inteventions.

Domain	**Risk of bias**			**Support for judgement**	**Location in text**
	Low risk	High risk	Unclear risk		*(pg & ¶/fig/table)*
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					
Blinding of participants and personnel *(performance bias)*				**Outcome group: all/**	
(if required)				**Outcome group:**	
Blinding of outcome assessment *(detection bias)*				**Outcome group: all/**	

(Continued)

(if required)	**Outcome group:**
Incomplete outcome data *(attrition bias)*	
Selective outcome reporting? *(reporting bias)*	
Other bias	
Notes:	

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomly assigned		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other treatments received *(additional to study intervention)*		
Other relevant socio-demographics		
Subgroups measured		
Subgroups reported		

(Continued)

Notes:

7. Intervention groups

Copy and paste table for each intervention group and for each comparison group.

Intervention group

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomly assigned to group		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. number, profession, training, ethnicity, etc., if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as a result of intervention)*		
Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		
Notes:		

Comparison group

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomly assigned to group		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. number, profession, training, ethnicity, etc., if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as a result of intervention)*		
Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		
Notes:		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1. Duration of anaesthesia

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		

(Continued)

Person measuring/reporting	
Unit of measurement *(if relevant)*	
Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for intention-to-treat (ITT) analysis)*	
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*	
Power	
Notes:	

Outcome 2. Adverse outcomes

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for intention-to-treat (ITT) analysis)*		
Assumed risk estimate		

(Continued)

(*e.g. baseline or population risk noted in Background)*
Power
Notes:

Outcome 3. Cost analysis

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data *(e.g. assumptions made for intention-to-treat (ITT) analysis)*		
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*		
Power		
Notes:		

Outcome 4. Duration of postoperative pain relief

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		

(Continued)

Time points measured	
Time points reported	
Outcome definition *(with diagnostic criteria if relevant)*	
Person measuring/reporting	
Unit of measurement *(if relevant)*	
Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	Yes No Unclear
Imputation of missing data *(e.g. assumptions made for intention-to-treat (ITT) analysis)*	
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*	
Power	
Notes:	

Outcome 5. Reduced bleeding during surgery

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?		

(Continued)

	Yes	No	Unclear
Imputation of missing data *(e.g. assumptions made for intention-to-treat (ITT) analysis)*			
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*			
Power			
Notes:			

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome 1. Adverse outcomes

	Description as stated in report/paper				**Location in text** *(pg & ¶/fig/table)*
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis					

(Continued)

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Dichotomous outcome 2. Reduced bleeding during surgery

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Comparison		
Outcome		
Subgroup		
Time point *(specify whether from start or end of intervention)*		

Results	**Intervention**		**Comparison**	
	No. events	No. participants	No. events	No. participants
No. missing participants and reasons				
No. participants moved from other group and reasons				
Any other results reported				
Unit of analysis				
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*				

(Continued)

Reanalysis required? *(specify)*	Yes No Unclear
Reanalysis possible?	Yes No Unclear
Reanalysed results	
Notes:	

Continuous outcome 1. Duration of anaesthesia

	Description as stated in report/paper						Location in text (pg & ¶/fig/table)
Comparison							
Outcome							
Subgroup							
Time point *(specify whether from start or end of intervention)*							
Post intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis							
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*							
Reanalysis required? *(specify)*	Yes No Unclear						
Reanalysis possible?							

(Continued)

	Yes	No	Unclear
Reanalysed results			
Notes:			

Continuous outcome 2. Cost analysis

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Comparison		
Outcome		
Subgroup		
Time point *(specify whether from start or end of intervention)*		
Post intervention or change from baseline?		

Results

Intervention			Comparison		
Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants

No. missing participants and reasons	
No. participants moved from other group and reasons	
Any other results reported	
Unit of analysis	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)* Yes No Unclear	
Reanalysis possible? Yes No Unclear	

(Continued)

Reanalysed results	
Notes:	

Continuous outcome 3. Duration of postoperative pain relief

	Description as stated in report/paper						Location in text (pg & ¶/fig/table)
Comparison							
Outcome							
Subgroup							
Time point *(specify whether from start or end of intervention)*							
Post intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis							
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*							
Reanalysis required? *(specify)*	Yes	No	Unclear				
Reanalysis possible?	Yes	No	Unclear				
Reanalysed results							
Notes:							

10. Applicability

Have important populations been excluded from the study? *(consider disadvantaged populations and possible differences in the intervention effect)*	Yes No Unclear
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	Yes No Unclear
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	Yes No Unclear
Notes:	

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

WHAT'S NEW

Date	Event	Description
4 November 2020	Amended	Minor updates to Background section of Review. Several updated references added.

HISTORY

Protocol first published: Issue 7, 2013
Review first published: Issue 3, 2015

CONTRIBUTIONS OF AUTHORS

Hemanshu Prabhakar (HP) Santosh Rath (SR), Mani Kalaivani (MK), Neel Bhanderi (NB).

Conceiving the review: SR.

Co-ordinating the review: HP, SR.

Undertaking manual searches: HP, NB.

Screening search results: HP, NB.

Organizing retrieval of papers: HP, SR.

Screening retrieved papers against inclusion criteria: HP, SR.

Appraising quality of papers: HP, NB.

Abstracting data from papers: HP, NB.

Writing to authors of papers for additional information: HP.

Providing additional data about papers: HP.

Obtaining and screening data on unpublished studies: HP.

Providing data management for the review: HP, SR.

Entering data into Review Manager (RevMan 5.3): HP, NB.

Interpreting RevMan statistical data: HP, MK.

Performing other statistical analyses not using RevMan: MK.

Interpreting data: HP, MK.

Making statistical inferences: MK.

Writing the review: HP.

Securing funding for the review: not applicable.

Performing previous work that served as the foundation of the present study: not applicable.

Serving as guarantor for the review (one review author): HP.

Taking responsibility for reading and checking the review before submission: HP, SR.

DECLARATIONS OF INTEREST

Hemanshu Prabhakar: none known.

Santosh Rath: none known.

Mani Kalaivani: none known.

Neel Bhanderi: none known.

SOURCES OF SUPPORT

Internal sources

- All India Institute of Medical Sciences, New Delhi, India

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between Prabhakar 2013 and review.

- A new review author (Neel Bhanderi) has joined the review team.
- We amended the inclusion criteria to include studies 'that compared the use of adrenaline with lidocaine and plain lidocaine' from the original statement in the protocol, which included studies that compared 'use of lidocaine with and without adrenaline'.
- We did not extract any numerical data from the graphs or figures.

NOTES

We would like to thank Jane Cracknell (Managing Editor of the Cochrane Anaesthesia Review Group (CARG)) for guiding us through this protocol (Prabhakar 2013) and Karen Hovhannisyan (CARG Trials Search Co-ordinator) for preparing our search strategy. We would like to thank Ronan O'Sullivan (Content Editor), Cathal Walsh (Statistical Editor) and Saeed Chowdhry, Don Lalonde and Vaughan Thomas (Peer Reviewers) for help and editorial advice provided during preparation of this protocol for a systematic review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthetics, Local; Emergencies; *Epinephrine; Finger Injuries [*surgery]; Fingers [*surgery]; *Lidocaine; Nerve Block [*methods]; Randomized Controlled Trials as Topic; Toes [*injuries] [*surgery]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Infant; Male