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Review

Commonly-used versus less commonly-used methods in the loss of resistance technique for identification of the epidural space: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Study objective: To summarize the efficacy of less-commonly used modern methods (e.g. epidrum, lidocaine, acoustic device, Macintosh balloon) compared to more commonly-used methods (i.e. air, saline, both) in the loss of resistance technique for identification of the epidural space.
Design: A systematic review.
Setting: A hospital-affiliated university.
Measurements: The following databases were searched: PubMed, CENTRAL, EMBASE, and LILACS. We used the GRADE approach to rate overall certainty of the evidence.
Results: Eight randomized trials including 1583 participants proved eligible. Results suggested a statistically significantly reduction in inability to locate the epidural space (RR 0.29, 95% CI 0.11, 0.77; P = 0.01; I^2 = 60%, risk difference (RD) 104/1000, moderate quality evidence), accidental intravascular catheter placement and accidental subarachnoid catheter placement (RR 0.35, 95% CI 0.21, 0.59; P < 0.0001; I^2 = 0%, risk difference (RD) 108/1000, moderate quality evidence), and unblocked segments (RR 0.37, 95% CI 0.18, 0.77; P = 0.008; I^2 = 0%, risk difference (RD) 56/1000, moderate quality evidence) with the use of epidrum, lidocaine, acoustic device, or modified Macintosh epidural balloon methods in comparison to air. Compared to saline, lidocaine presented higher rates of reduction in the inability to locate the epidural space (RR 0.31, 95% CI 0.12, 0.82; P = 0.02; I^2 = not applicable).
Conclusions: Moderate-quality evidence shows that less commonly-used modern methods such as epidrum, lidocaine and acoustic devices, are more efficacious compared to more commonly-used methods (i.e. air, saline, both) in terms of the loss of resistance technique for identification of the epidural space. These findings should be explored further in the context of the clinical practice among anaesthesiologists.

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1. Introduction

The establishment of epidural anesthesia depends on accurate identification of the epidural space. The loss of resistance (LOR) technique for identification of the epidural space seems to be the most commonly used method for the identification of the epidural space [1,2].

The selection between air and saline in the LOR technique for identification of the epidural space has been headed by know-how and individual preference of anesthesiologists [2,3]. In 1998, a study showed that 53% of the anesthesiologists interviewed used saline, 37% used air, 6% used both, and only 3% used alternative methods in conducting the LOR technique [2–4].

However, both methods also present disadvantages [3,5,6]. Epidural injection of air implies some hazards [7–11], and air bubbles in the epidural space can result in only partial analgesia [12]. Also, complications may increase with the use of large volumes of air when validation of the correct placement of the epidural needle is needed [13,14]. Furthermore, the use of saline is reported to slow the onset and reduce the quality of epidural analgesia [15,16]. Thus, there is no consensus as to whether an air or a liquid medium should be used for identifying the epidural space when using a loss of resistance technique. It is also possible that the techniques not widely used today such as epidrum, Macintosh balloon, advancing needle by indirect means such as hanging drop, or even other liquids such as lidocaine can improve quality of analgesia, and reduce complications associated with loss of resistance technique.

With a variety of methods introduced over the last three decades [2, 17–22] to improve the success of the puncture procedure [23,24], the literature remains conflicted in terms of the most appropriate strategy for epidural catheter placement in patients undergoing surgical procedures, women in obstetrical labor and patients with analgesia in the postoperative period.

Over the years, many devices have been designed to improve the success of the puncture procedure [25,26]; however, none of them is widely used today. Among them, there are the epidrum, which is a single-use device that is placed between a luer syringe and epidural needle, and it provides the user with a visual signal when the epidural needle enters the epidural space; the acoustic devices [27]; and the use of lidocaine [28].

In a recent Cochrane systematic review [2], authors concluded that there was no difference between air and saline in the LOR technique for identification of the epidural space; however, the generalizability of these findings might be compromised, given that the majority of the synthesized data was obtained from pregnant women.

The methods used in identification of the epidural space are extremely important for effective anesthesia and to avoid potential complications, such as perforation of the dura mater, epidural hematomas (due to lesions of vessels from the needle and catheter), patchy blocks, low back pain and air venous embolisms [2,29–34].

To the best of our knowledge, a systematic synthesis of randomized controlled trial (RCT) data comparing more commonly-used versus less commonly-used methods in the LOR technique in terms of their efficacy and associated complications has not been conducted. As such, the purpose of this systematic review was to evaluate the efficacy and safety of more commonly-used methods (i.e. air or saline, or both) versus less commonly-used methods (e.g. epidrum, lidocaine, acoustic device, Macintosh balloon) in the LOR technique for identification of the epidural space.

2. Materials and methods

The Cochrane Handbook for Intervention Reviews [35] guided our choice of methods. This systematic review of the literature on interventional studies was conducted in accordance with the PRISMA (Preferred Reposting Items for Systematic Reviews and Meta-analysis) statement [36].

2.1. Eligibility criteria

We considered all RCTs and quasi-RCTs evaluating one or more commonly-used methods (i.e. air or saline, or both) versus one or more less commonly-used methods, such as epidrum, lidocaine, acoustic device, Macintosh balloon, or the combination of a commonest methods with a not widely used today device (e.g. air and lidocaine), in the LOR technique for identification of the epidural space.

Eligible studies reported one or more of the following: a) inability to locate the epidural space, defined as inability to identify the epidural space and/or unintentional dural puncture by epidural needle; b) accidental intravascular catheter placement and/or accidental subarachnoid catheter placement; c) unblocked segments; d) inadvertent dural puncture; e) adverse events, such as headache or migraine, neck pain, subcutaneous emphysema, difficulty in advancing the catheter, hypotension,

Table 1
Search strategy for all electronic databases.

(Air OR Na Sodium Chloride OR NaCl Sodium Chloride OR Saline Solution OR Saline OR Epidrum OR 2-2EtN-2MePhAcN OR Lignocaine OR 2-(Diethylamino)-*N*-(2,6-Dimethylphenyl)Acetamide OR Lidocaine Carbonate (2:1) OR Lidocaine Carbonate OR Lidocaine Hydrocarbonate OR Lidocaine Hydrochloride OR Lidocaine Monohydrochloride OR Lidocaine Monoacetate OR Xyloneural OR Strathmann Brand of Lidocaine Hydrochloride OR Lidocaine Sulfate (1:1) OR Octocaine OR Novocol Brand of Lidocaine Hydrochloride OR Xylesthesin OR Xylocaine OR Astrazeneca Brand of Lidocaine OR Xylocitin OR Jenapharm Brand of Lidocanine Hydrochloride OR Dalcaine OR Monohydrate Lidocaine Monohydrochloride OR Acoustic device OR acoustic devices) AND (Epidural analgesia OR epidural anaesthesia OR Peridural Anesthesia OR Extradural Anesthesia OR Epidural Spaces OR Epidural Space)

*Restricted to humans and clinical trials.

paresthesia, dysesthesia, and catheter replacement and/or reposition; and f) pain relief.

Systematic reviews of eligible RCTs and quasi-RCTs were included for the identification of eligible studies through a review of reference lists. Animal studies, case reports and narrative review articles were excluded.

2.2. Data source and searches

The search was performed in the following electronic databases: Cochrane Database of Clinical Trials (CENTRAL, 2016, issue 4), PubMed (1966–2016), EMBASE (1980–2016), and LILACS (1982–2016). The databases were searched for available published and unpublished studies from inception through to April 21, 2016.

The search was conducted using multiple combinations of the following key words: “air”, “saline solution”, “epidrum”, “lidocaine”, “analgesia” and “epidural space” (Table 1). No restrictions were placed on language, year of publication or publication status.

In addition, a manual search of the reference lists of potential primary studies was conducted, and several major anesthesiology journals were hand-searched for additional eligible studies.

2.3. Selection of studies

Using pre-standardized screening forms and protocols, teams of two reviewers independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated these studies for eligibility. Reviewers resolved disagreement through discussion, with third party adjudication if necessary.

2.4. Data extraction and risk of bias assessment

Three pairs of reviewers independently extracted the following data using a pre-standardized data extraction form: characteristics of the study design; participants; interventions; outcomes event rates and follow-up. Authors of eligible studies were contacted by reviewers to identify missing data and confirm data accuracy of eligible studies.

Reviewers independently assessed risk of bias by using a modified version of the Cochrane Collaboration's tool [37] examining nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in previously cited domains [38]. For incomplete outcome data, we considered loss to follow-up of $<10\%$ and a difference of $<5\%$ in missing data between intervention and control groups as low risk of bias.

2.5. Certainty of evidence

The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of evidence for each outcome as high, moderate, low, or very low [39]. Detailed GRADE guidance was used to assess overall risk of bias [40], imprecision [41], inconsistency [42], indirectness [43] and publication bias [44], and results were summarized in an evidence profile.

2.6. Data synthesis and statistical analysis

We calculated pooled risk ratios (RRs) for dichotomous outcomes with the associated 95% CIs using random-effects models with the Mantel-Haenszel statistical method. We addressed variability in results across studies by using I^2 statistic and the P value obtained from the Cochran chi square test. Our primary analyses were based on eligible patients who had reported outcomes for each study (complete case analysis).

We performed subgroup analyses according to the different methods: combination techniques (air and lidocaine) versus air; not widely used today techniques versus commonest methods (saline,

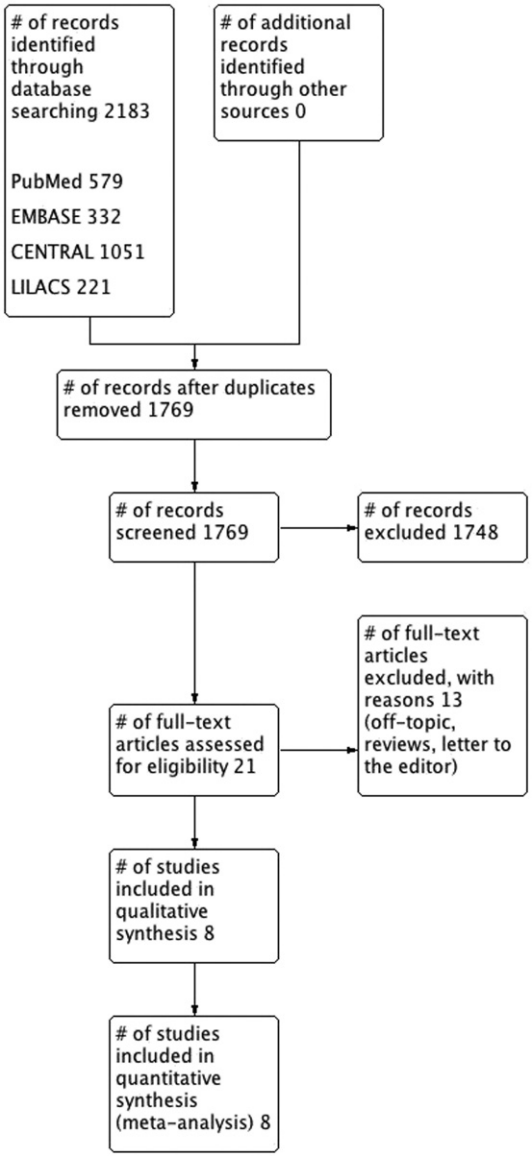

Fig. 1. PRISMA diagram of included studies.

air); or one type of widely used today techniques versus another. We planned to perform separate analyses for comparisons with different populations consisting of pregnant and non-pregnant patients. We planned to assess publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [45].

3. Results

3.1. Search results

Following the removal of duplicate hits, we identified a total of 1769 unique citations through database searches. Title and abstract screening was conducted, leaving 21 potentially-eligible citations for which full-text articles were obtained and reviewed in duplicate. Fourteen studies were excluded, as they were reviews, letters to the editor, or did not address one or more aspects of the research question. A total of eight studies [20,28,46–51] with a total of 1583 participants were deemed eligible for inclusion. No additional eligible studies were identified based on hand-searching of major anesthesia journals or manual review of reference lists of relevant primary studies and systematic reviews (Fig. 1).

3.2. Characteristics of included studies

Table 2 describes study characteristics regarding setting, number of participants, mean age, gender, eligibility criteria, and follow-up. All included studies [20,28,46–51] were parallel trials. Three studies [20,47,

Table 2
Study characteristics related to setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up.

Author, year	Location	No.[a] participants	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up
Deigahn 2015 [46]	Ireland	300	Epidrum: not reported LOR: not reported	0 0	Parturient requesting epidural analgesia for labor	Patients younger than 18 or those unable to give informed consent	24–48 h
Kim 2012 [47]	Korea	108	Epidrum[b]: 45 LOR (air, saline or both): 45.4	27.7 29.6	Patients between 17 and 68 years ASA physical status I or II who were scheduled for elective gynecologic or orthopedic surgery under combined spinal-epidural anesthesia	Patients with contraindications for combined spinal-epidural anesthesia, including coagulopathy, local skin infection, and uncorrected hypovolemia	Not reported
Sawada 2012 [20]	Japan	80	Epidrum[b]: 54.3 LOR or the hanging drop: 51.7	37.5 40	Adult patients ASA I or II between 22 and 86 years scheduled for elective surgery under lombar epidural anesthesia	Patients with lumbar spinal disease, known coagulation disorders or severe obesity (BMI > 35 kg/m^2)	Not reported
Hirabayashi 2011 [48]	Japan	40	Epidrum[b]: 35.0 Saline: 32.0	0 0	Healthy parturients (gestation age, <35 weeks) scheduled for elective cesarean section under combined spinal-epidural anesthesia	Coagulopathy, deformities in vertebra	Not reported
Fyneface-Ogan 2008 [49]	Nigeria	50	Modified Macintosh epidural balloon (Vygon): 29.2 Air: 30.08	0 0	Parturient requesting epidural analgesia for labor, ASA Class I-II	Patients with ASA physical status II or greater, pre-eclampsia/eclampsia, morbid obesity (blood mass index > 35 kg/m^2), a history of drug or alcohol abuse, heavy smoking or abnormal liver, hepatic, or hematological test results. Also were excluded if clinicians suspected accidental dural puncture or catheterization of a blood vessel	1 h after epidural catheter insertion and at the second stage of labor
Elhakim 2006 [50]	Egypt	440	Acoustic Device: 27.3 Air: 26.8	0 0	Laboring ASA status 1 or 2 woman with cephalic presentation pregnancy at term and who requested epidural analgesia	Patients with known coagulation, liver, and neuromuscular disorders, history of spinal surgery or trauma, hypersensitivity to amide local anesthetics, morbid obesity (BMI > 35 kg/m^2), and skin lesions at the site of lumbar puncture	Not reported
Evron 2004 [28]	Not reported	547	Lidocaine 3 ml 2%: 28.0 Air: 28.0 Sequential use of air and lidocaine: 27.0	0 0 0	Nulliparous laboring ASA status I and II women with singketin ceohakic presentation at term and who requested epidural analgesia	ASA physical status III or greater, preemclampsia, morbid obesity (body mass index > 35 kg/m^2), a history of drug or alcohol abuse, heavy smoking, or abnormal liver, hepatic, or hematological test results	1 h after epidural catheter insertion and at the second stage of labor
Rolbin 1990 [51]	Canada	200	Lidocaine 3 ml, 1,5%: not reported No fluid (air): not reported Normal saline, 3 ml: not reported	0 0 0	Patients in labor requesting epidural anesthesia for the first stage of labor	Not reported	20 min after the insertion of the epidural needle and within 24 h of delivery

No.: number; RCT: randomized controlled trial; ml: milliliter; LOR: loss of resistance.
[a] Randomized participants.
[b] Epidrum: is 2.5–2 cm in size and consists of a hard plastic body chamber, an injection port with a one way valve, an outlet port to connect to the epidural needle, and a soft, thin silicon membrane diaphragm on top of the device.

48] were conducted largely in Asia (one in Korea, and two in Japan), one in Ireland [46], one in Egypt [50], one in Canada [51], and one in Nigeria [49]. Evron et al. 2004 did not report the setting of their study [28]. Trial sample sizes ranged from 40 participants [48] to 547 participants [28]. Participants were typically females between the ages of 20 and 60 years. Studies followed participants from 20 min [51] to 48 h [46] post-needle insertion (Table 2).

Table 3 describes study characteristics related to intervention and comparator groups, and assessed outcomes. Of the eight RCTs, three compared epidrum to air [20,46,47]; two compared epidrum to saline [47,48]; one compared modified Macintosh epidural balloon to air [49]; one compared acoustic device to air; one compared lidocaine 2% to air [28]; one compared lidocaine 1.5% to air or saline [51]; and one compared the acoustic device to air [50] (Table 3).

3.3. Risk of bias in individual studies

Fig. 2 and Table 4 describe the risk of bias assessment for the RCTs. Allocation concealment was a major risk of bias limitation across all eligible RCTs [20,28,46–51]. Other issues with risk of bias among eligible RCTs were random sequence generation [20,28,47–51], lack of blinding of participants, caregivers, data collectors, and statisticians [20,28,47–49,51], and lack of blinding of outcome assessors [20,47–49,51].

We considered the Fyneface-Ogan 2008 study [49] as high risk of bias for blinding of outcome assessors, because although authors reported that there was a blinded anaesthetist that assessed some outcomes such as the existence of unblocked segments and the extent of sensory blockade, an attending anaesthetist that was not blinded noted paraesthesia during insertion of the catheter, inability to advance the catheter, and intravenous or subarachnoid cannulation (Fig. 2, Table 4).

3.4. Effectiveness of interventions

3.4.1. Meta-analysis of inability to locate the epidural space

Results from seven RCTs [20,28,46–47,49–51] suggested a statistically significantly reduction in inability to locate the epidural space using epidrum, lidocaine, acoustic device, or modified Macintosh epidural balloon over air, or hanging drop (RR 0.29, 95% CI 0.11, 0.77; P = 0.01; I^2 = 60%, risk difference (RD) 104/1000, moderate quality evidence) (Fig. 3, Table 5). A plausible sensitivity analysis without the Deighan et al. 2015 study [46] yielded results that were consistent with the primary analysis, decreasing the inconsistency among plotted studies and suggesting an even higher reduction in inability to locate the epidural space with less commonly-used methods in comparison to air or the hanging drop (RR 0.23, 95% CI 0.11, 0.49; P = 0.0001; I^2 = 36%) (Appendix Fig. 1). Certainty in evidence was rated down to moderate because of inconsistency and risk of bias due to allocation concealment limitations across all studies, and lack of blinding of participants, caregivers, data collectors, statisticians [20,28,47,49,51] and outcome assessors [20,47–49,51] (Fig. 2, Table 5).

Results from a single study [28] also suggested a statistically significantly reduction in inability to locate the epidural space with the use of combination methods (i.e. air and lidocaine) over air (RR 0.20, 95% CI 0.09, 0.48; P = 0.0003; I^2 = not applicable) (Fig. 3). Additional results related to a subgroup meta-analysis comparing less commonly-used techniques versus saline also found also a statistically significance difference favouring the use of lidocaine (RR 0.31, 95% CI 0.12, 0.82; P = 0.02; I^2 = not applicable) (Fig. 3).

3.4.2. Meta-analysis of accidental intravascular catheter placement and accidental subarachnoid catheter placement

Results from two RCTs [28,50] suggested a statistically significantly reduction in accidental intravascular catheter placement and accidental subarachnoid catheter placement with the use of lidocaine or acoustic device over air (RR 0.35, 95% CI 0.21, 0.59; P < 0.0001; I^2 = 0%, RD 108/1000, moderate quality evidence) (Fig. 4; Table 5). Certainty in evidence was rated down to moderate because of risk of bias due to lack of blinding of participants, caregivers, data collectors, statistician [27], and allocation concealment [48] (Fig. 2, Table 5).

Results from a single study [28] also suggested a statistically significantly reduction in accidental intravascular catheter placement and/or accidental subarachnoid catheter placement with the use of combination methods (air and lidocaine) over air (RR 0.46, 95% CI 0.25, 0.84; P = 0.01; I^2 = not applicable) (Fig. 4).

Table 3
Study characteristics related to the description of intervention, control group, and assessed outcomes.

Author, year	Description of intervention group (randomized patients, n)	Description of control groups (randomized patients, n)	Measured outcomes
Deighan 2015 [46]	Epidrum (n = 150)	LOR (not specified) (n = 150)	Dural puncture; number of attempts taken to site epidural; failure (defined as being unable to site the epidural catheter after three attempts) to site epidural requiring a second operator; and failure of epidural analgesia (defined as failure to obtain a sensory block after initial local anaesthetic loading dose, resulting in the epidural catheter being re-sited).
Kim 2012 [47]	Epidrum[a] (n = 54)	LOR (air, saline or both) (n = 54)	Failure; time; epidural depth (cm, L3–4 and L4–5 interspace); dural puncture; ease score of identification (operator and observer); and satisfaction score of operator.
Sawada 2012 [20]	Epidrum[a] (n = 40)	LOR (not specified) or the hanging drop (n = 40)	Epidural catheterization; clinical effects of epidural anesthesia; accidental dural puncture; and time to identify epidural space.
Hirabayashi 2011 [48]	Epidrum[a] (n = 20)	Saline (n = 20)	Inability to locate the epidural space; accidental intravascular catheter placement and/or accidental subarachnoid catheter placement; inadvertent dural puncture; and morbidities.
Fyneface-Ogan 2008 [49]	Modified Macintosh epidural balloon (Vygon®) (n = 25)	Air (n = 25)	Easy of epidural identification; accidental dural puncture; quality of block; post-dural puncture headache; delay in second stage; shivering.
Elhakim 2006 [50]	Acoustic device (n = 220)	Air (n = 220)	Side effects and complications of epidural analgesia defined as difficult epidural catheter insertion; patients with unblocked; accidental intravascular catheter; accidental dural puncture; postural headache; hypotension; postpartum urinary retention; transient neurological deficit; persistent neurological deficit; and characteristics of epidural analgesia.
Evron 2004 [28]	Lidocaine 3 ml, 2% (n = 185)	Air (n = 180) Air and lidocaine (n = 182)	Side effects and complications of epidural anesthesia defined as difficult epidural catheter insertion; accidental intravascular catheter placement; patients with unblocked segments; accidental dural puncture; postdural puncture headache; transient neurological deficit; persistent neurological deficit; postpartum urinary retention; hypotension and; characteristics of epidural analgesia.
Rolbin 1990 [51]	Lidocaine 3 ml, 1.5% (n = 68)	Air (n = 77) Saline 3 ml (n = 55)	Complications of the catheter insertion such as blood in catheter; paresthesiae; involuntary movement; threaded easily (inability to locate epidural space); and pain relief.

n: number; cm: centimeters; ml: milliliters; LOR: Loss of resistance technique.
[a] Epidrum: is 2.5–2 cm in size and consists of a hard plastic body chamber, an injection port with a one way valve, an outlet port to connect to the epidural needle, and a soft, thin silicon membrane diaphragm on top of the device.

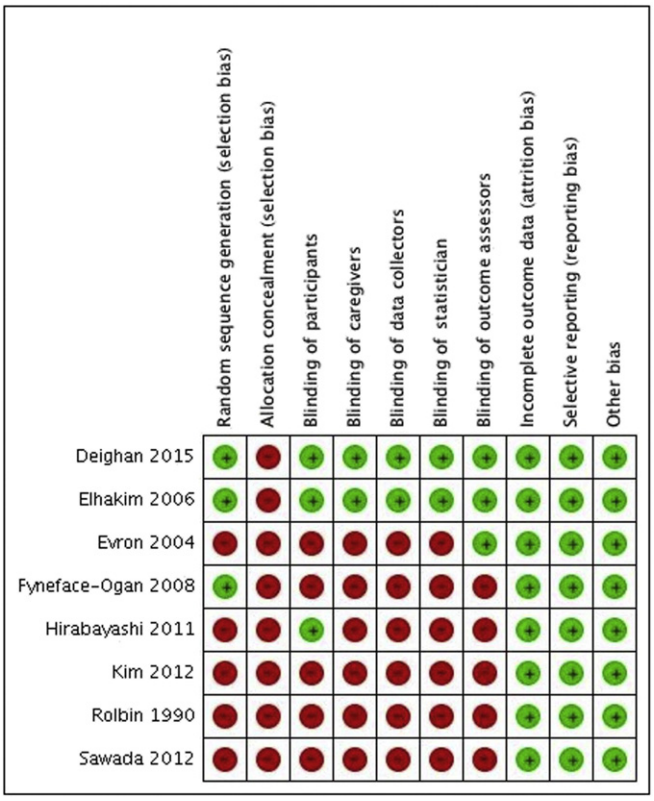

Fig. 2. Risk of bias in individual studies. Note: "probably yes" is grouped into "yes", and "probably no" is grouped into "no".

3.4.3. Meta-analysis of unblocked segments

Results from three RCTs [28,49,50] suggested a statistically significantly reduction of unblocked segments with the use of lidocaine, acoustic device, or modified Macintosh epidural balloon over air (RR 0.37, 95% CI 0.18, 0.77; P = 0.008; I^2 = 0%, RD 56/1000, moderate quality evidence) (Fig. 5, Table 5). Certainty in evidence was rated down to moderate because of risk of bias due to lack of blinding of participants, caregivers, data collectors and statisticians [28,49], and allocation concealment [49,50] (Fig. 2, Table 5).

Results from a single study [28] comparing combination methods (air and lidocaine) versus air found no statistically significance difference (RR 0.33, 95% CI 0.11, 1.00; P = 0.05; I^2 = not applicable) (Fig. 5).

3.4.4. Meta-analysis of inadvertent dural puncture

Results from six RCTs [20,28,46,49–50] found no statistically significance difference related to inadvertent dural puncture comparing epidrum, lidocaine, acoustic device, or modified Macintosh epidural balloon versus air (RR 0.27, 95% CI 0.05, 1.14; P = 0.26; I^2 = 51%, RD 14/1000, low quality evidence) (Fig. 6, Table 5). Certainty in evidence was rated down to low because of inconsistency and risk of bias issues related to allocation concealment limitations across all studies, and lack of blinding of participants, caregivers, data collectors and statisticians [20,28,47,49] and outcome assessors [20,47,49] (Fig. 2, Table 5).

Results from a single study [28] suggested a statistically significantly reduction in the inadvertent dural puncture with the use of combination methods (air and lidocaine) over air (RR 0.02, 95% CI 0.00, 0.26; P = 0.004; I^2 = not applicable) (Fig. 6).

3.4.5. Meta-analysis of adverse events

Results from three RCTs [49–51] suggested no statistically significant difference related to adverse events with the use of acoustic device, modified Macintosh epidural balloon, or lidocaine versus air (RR 0.56, 95% CI 0.19, 1.68; P = 0.30; I^2 = 36%, RD 9/1000, moderate quality evidence) (Fig. 7, Table 5). Certainty in evidence was rated down to moderate because of risk of bias due to lack of blinding of participants, caregivers, data collectors, statisticians, and outcome assessors [35,37], and allocation concealment [49–51] (Fig. 2, Table 5).

Results related to a single study [51] comparing lidocaine versus saline found no statistically significance difference (RR 0.95, 95% CI 0.67, 1.34; P = 0.76; I^2 = not applicable) (Fig. 7).

4. Discussion

4.1. Main findings

Based on pooled data from eight randomized trials with 1583 participants, our systematic review found evidence for a reduction in inability to locate the epidural space, accidental intravascular catheter placement and/or accidental subarachnoid catheter placement, unblocked segments, and inadvertent dural puncture with the use of the less commonly-used methods (i.e. epidrum, lidocaine, acoustic device, or

Table 4
Risk of bias assessment.

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?[a]	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Deighan 2015 [46]	Definitely yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Probably yes
Kim 2012 [47]	Probably no	Probably no	Definitely no	Definitely no	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes
Sawada 2012 [20]	Probably no	Probably no	Probably no	Probably no	Definitely no	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes
Hirabayashi 2011 [48]	Probably no	Probably no	Probably yes	Definitely no	Definitely no	Probably no	Probably no	Definitely yes	Definitely yes	Definitely yes
Fyneface-Ogan 2008 [49]	Definitely yes	Probably no	Probably no	Definitely no	Probably no	Probably no	Definitely no	Definitely yes	Definitely yes	Probably yes
Elhakim 2006 [50]	Definitely yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Probably yes
Evron 2004 [28]	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Definitely yes	Probably yes
Robin 1990 [51]	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).
[a] Defined as <10% loss to outcome data or difference between groups <5% and those excluded are not likely to have made a material difference in the effect observed.

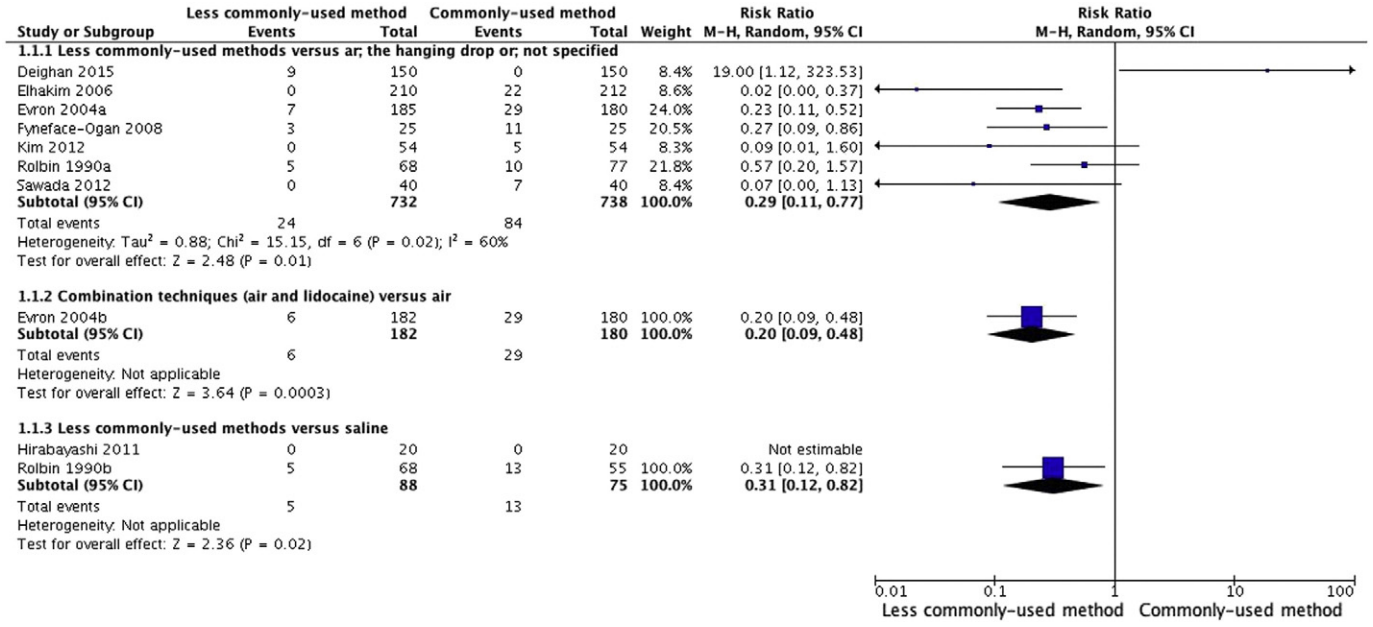

Fig. 3. Meta-analysis of inability to locate the epidural space.

modified Macintosh epidural balloon) relative to more commonly-used (air or saline, or both) (Figs. 3, 4, 5, 6). Moderate quality evidence supports the use of less commonly-used methods in the LOR technique for identification of the epidural space (Table 5). A plausible sensitivity analyses to assess the inconsistency associated with Deighan et al. 2015 study [46] yielded results that were consistent with the primary analysis, and also decreased the heterogeneity among studies plotted in the meta-analysis (Appendix Fig. 1).

A number of factors decreased our certainty in the estimates for inability to locate the epidural space. In particular, issues related to risk

Table 5
GRADE evidence profile: alternative techniques (epidrum, lidocaine, acoustic device, modified Macintosh epidural balloon) versus air for identification of the epidural space.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk (95% CI)	Anticipated absolute effects		OR Quality of evidence
No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Conventional	Alternative		Conventional	Alternative	
Inability to locate the epidural space											
1470 (7)	Serious limitations[a]	Serious limitations[b]	No serious limitations	No serious limitations	Undetected	84/738	24/732	0.29 (0.11–0.77)	104 per 1000[c]	74 fewer per 1000 (93 fewer to 24 fewer)	MODERATE
Accidental intravascular catheter placement and/or accidental subarachnoid catheter placement											
787 (2)	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	53/392	19/395	0.35 (0.21–0.59)	108 per 1000[c]	71 fewer per 1000 (86 fewer to 45 fewer)	MODERATE
Unblocked segments											
787 (2)	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	24/392	9/395	0.38 (0.18–0.82)	56 per 1000[c]	35 fewer per 1000 (46 fewer to 11 fewer)	MODERATE
Inadvertent dural puncture											
1325 (6)	Serious limitations[a]	Serious limitations[b]	No serious limitations	Serious imprecision[d]	Undetected	37/661	4/664	0.27 (0.05–1.56)	14 per 1000[c]	10 fewer per 1000 (13 fewer to 8 more)	LOW
Adverse events											
617 (3)	Serious limitations[a]	No serious limitations	No serious limitations	Serious imprecision[d]	Undetected	50/314	35/303	0.56 (0.19–1.68)	9 per 1000[c]	4 fewer per 1000 (7 fewer to 6 more)	MODERATE

[a] The large sample of studies include many that were ranked as high risk of bias in some of the categories analyzed.
[b] There was some heterogeneity among included studies.
[c] Baseline risk estimates for inability to locate the epidural space come from control arm of Elhakim 2006 [50] study (largest randomized trial in the meta-analysis).
[d] 95% CI for absolute effects include clinically important benefit and no benefit.

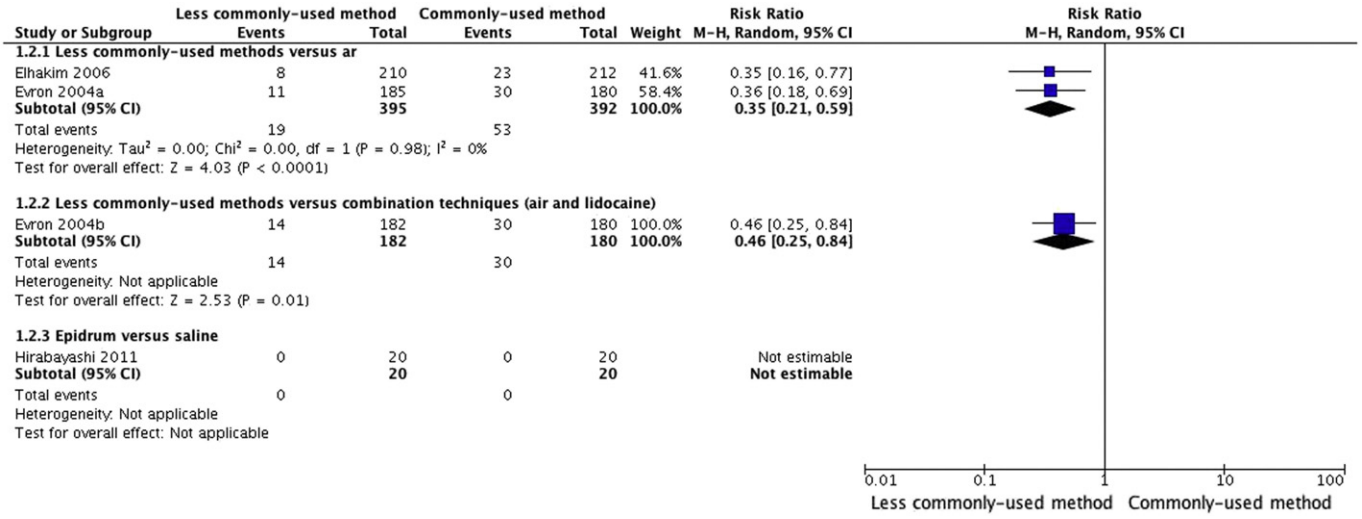

Fig. 4. Meta-analysis of accidental intravascular catheter placement and/or accidental subarachnoid catheter placement.

of bias decreased confidence in our estimates, including: lack of blinding of patients, health care providers and outcome adjudicators in a number of studies, lack of allocation concealment, and some inconsistency in two of the meta-analyses that may represent substantial heterogeneity (Figs. 3 and 6). There was no difference related to side effects comparing the alternative and conventional methods in the RCTs.

"To appropriately identify the epidural space, it is necessary to have adequate knowledge of the relevant anatomy. Use of air or saline has been controversial and widely variable amongst anaesthesiologists" [2]. However, "the inability to locate the epidural space (defined as inability to identify the epidural space and/or unintentional dural puncture by the epidural needle) also appears to be dependent on the amount of training the anaesthesiologist has undergone" [2]. Therefore, independent of the method used in the LOR technique, the identification of alternative potential techniques to access the epidural space may be necessary to avoid unnecessary complications such as paraesthesias, air venous embolisms, neurological complications, accidental punctures of the dura mater, total subarachnoid blocks, and pneumoencephaly.

Another variable which might influence the results independent of the technique used in the LOR technique is the "correlation between volume of anaesthetic injected by the epidural needle and successful catheter passage subsequently" [2]. Earlier studies have proven that "a large volume of local anaesthetics through the needle facilitates catheter placement, decreasing the chance of accidental intravascular or subarachnoid catheter placement" [2,52,53].

Finally, only one included study [48] described severe morbidities such as pneumonia, poor oxygenation and myocardial infarction; these outcomes are unlikely to be correlated with the application of either of the two LOR technique methods.

4.2. Strengths and limitations

Strengths of our review include: a comprehensive literature search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias; sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.

Limitations of our study include only eight studies being eligible despite a comprehensive search of four databases, prominent journals and the reference lists of all relevant primary studies and systematic reviews. Methodological quality was generally deemed to be unclear or low risk of bias across all included studies. The limited number of eligible studies prevented subgroup analyses from being conducted based on the characteristics of participants (e.g., pregnant vs. non-pregnant patients); the criteria for a minimum of six eligible studies, with at least three for each sub-group, was not met for any potential analysis.

Another limitation of this review is the fact that most data is focused on the use of epidrum, with varying patient populations, and data also comes from the subgroup analyses that included only one study. In considering the results of these studies together, it is important to consider that pregnant patients have a greater chance of epidural venous bleeding, dural puncture and headache than non-pregnant patients. Furthermore, orthopedic patients also differ in their likelihood of experiencing successful epidural insertion and complications.

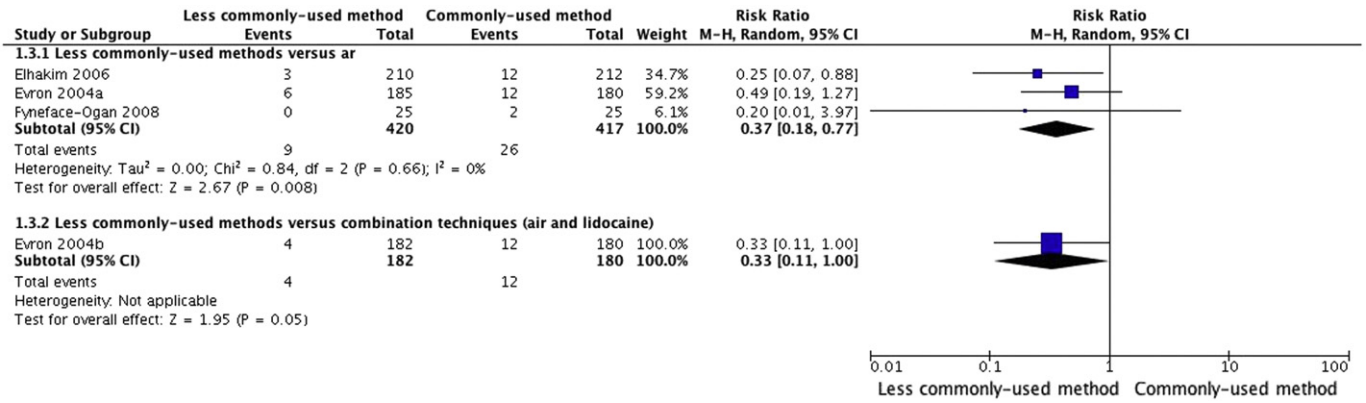

Fig. 5. Meta-analysis of unblocked segments.

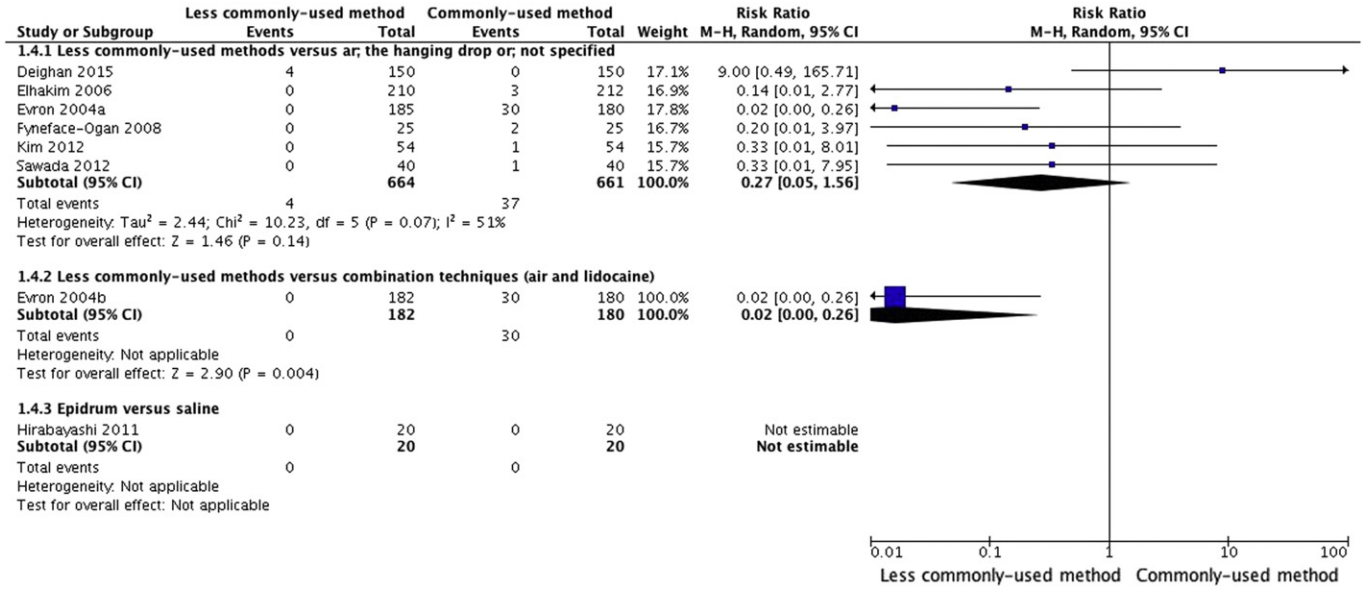

Fig. 6. Meta-analysis of inadvertent dural puncture.

One could argue that these limitations make the pooling of results we have undertaken inadvisable. On the other hand, the pooling does highlight the moderate-quality evidence of less commonly-used methods on the reduction in inability to locate the epidural space, a possibility that, until definitively refuted by randomized trials, needs consideration in policy debates regarding the loss of resistance technique for identification of the epidural space.

Finally, another limitation of this review is the potential for heterogeneity as the less commonly-used methods compared differ in terms of techniques. It is possible that analyzing these methods separately would have greater benefit. However, the fact of having insufficient number of included studies did not allow the complete statistical analysis that we had planned.

Although this review presents several limitations, the issue is whether one should dismiss these results entirely, or consider them bearing in mind the limitations. The latter represent our view of the matter.

4.3. Relation to prior work

The previous Cochrane review [2] comparing conventional methods in the LOR technique concluded "low-quality evidence shows that results do not differ between air and saline when the LOR technique is used to locate the epidural space" [2]. However, findings were limited by a trivial sample size and lack of standardization of results across studies, making a meta-analysis difficult to conduct.

4.4. Implications

Moderate-quality evidence shows that less commonly-used methods such as epidrum, lidocaine, acoustic devices, or modified Macintosh epidural balloon are more efficacious compared to more commonly-used methods (air, saline, or both) in terms of the LOR technique for identification of the epidural space. With regards to safety-related outcomes, moderate-quality evidence demonstrates that complications are relatively equal between both approaches.

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Conflicts of interest

The authors report no conflicts of interest. The funding agency played no role in the conduct of the research or preparation of the manuscript.

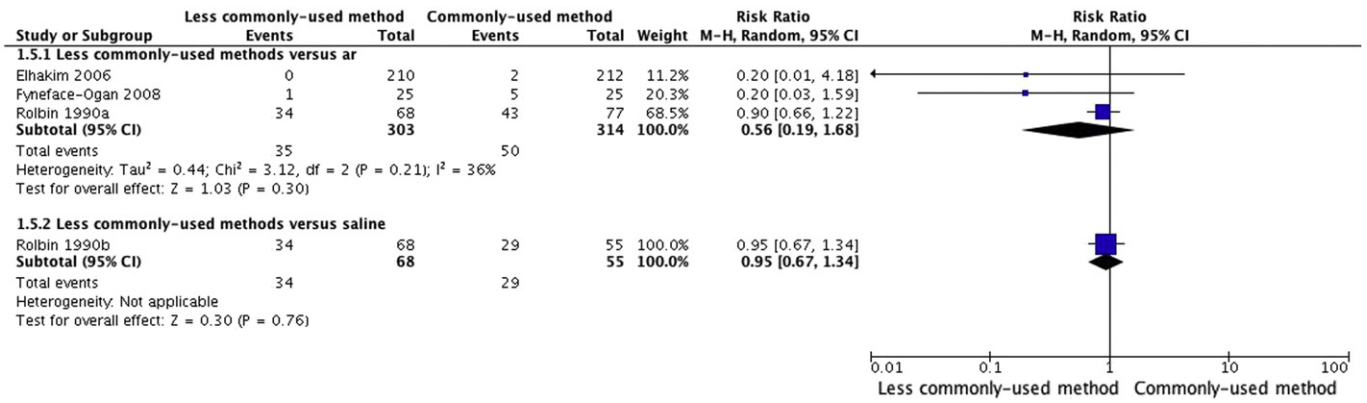

Fig. 7. Meta-analysis of adverse events.

Authors' contributions

Larissa Pierri Carvalho (LPC), Arnav Agarwal (AA), Flávio T Kashiwagi (FTK), Ione Corrêa (IC), José Eduardo G Pereira (JEGP), Regina El Dib (RED).

Author Contributions: conceptualization: RED.
Author Contributions: methodology: JEGP RED.
Author Contributions: software: LPC RED.
Author Contributions: validation: LPC JEGP RED.
Author Contributions: formal analysis: LPC JEGP RED.
Author Contributions: investigation: LPC FTK JEGP RED.
Author Contributions: resources: IC.
Author Contributions: data curation: LPC FTK JEGP RED.
Author Contributions: writing (original draft preparation): LPC AA IC JEGP RED.
Author Contributions: writing (review and editing): LPC AA FTK IC JEGP RED.
Author Contributions: visualization: JEGP RED.
Author Contributions: supervision: JEGP RED.
Author Contributions: project administration: RED.
Author Contributions: funding acquisition:

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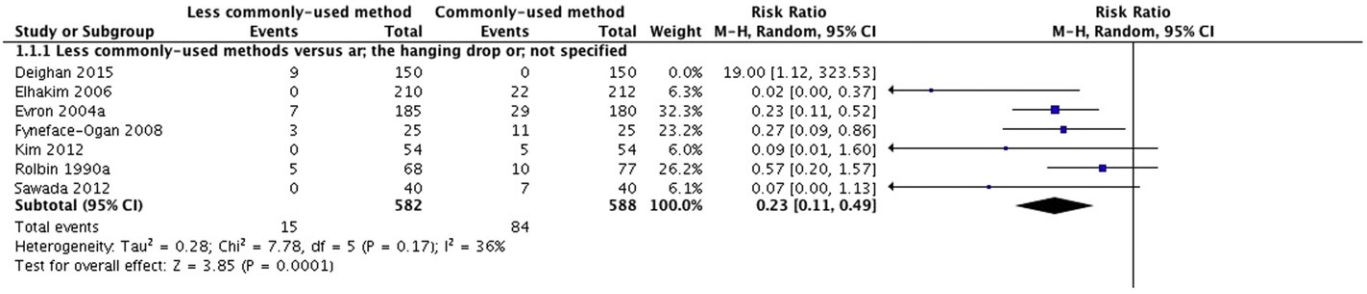
Appendix A



Appendix Fig. 1. Sensitivity analysis of inability to locate the epidural space.

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