Epidural Space Identification: A Meta-Analysis of Complications After Air Versus Liquid as the Medium for Loss of Resistance

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BACKGROUND: The best method for identifying the epidural space for neuraxial blocks is controversial. We conducted this meta-analysis to test the hypothesis that loss of resistance with liquid reduces complications with epidural placement.

METHODS: The MEDLINE, EMBASE, and Cochrane databases were searched for prospective, randomized studies comparing air versus liquid as the medium for loss of resistance during epidural space identification in adults. Data were abstracted from 5 studies (4 obstetric and 1 nonobstetric) (n = 4422 patients) that met inclusion criteria and analyzed for the following 6 outcomes: difficult catheter insertion, paresthesia, intravascular catheter insertion, accidental dural puncture, postdural puncture headache, and partial block.

RESULTS: The overall risk differences for adverse outcome between the different mediums were not statistically different for the obstetric population. A small, but statistically significant, risk difference for postdural puncture headache was observed when fluid was used during epidural placement for chronic pain management.

CONCLUSION: Larger studies that overcome limitations of heterogeneity across studies and a relatively infrequent occurrence of complications are required to determine the optimal medium for loss of resistance during epidural block.

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The safety and effectiveness of epidural anesthesia and analgesia depend on reliable epidural needle placement. The loss of resistance technique, used since the early 20th century and the most common method used for epidural space identification,[1,2] relies on sudden loss of resistance to the injection of a liquid medium (usually saline [with or without an air bubble]) or air as the tip of the Tuohy needle traverses the ligamentum flavum and enters the epidural space.[1–3]

A survey of 500 obstetric anesthesiologists, conducted in the United Kingdom (1998), found that of the 404 surveys returned only 33% of anesthesiologists had learned the loss of resistance technique using saline.[2] However, 53% were using a saline loss of resistance technique in their daily clinical practice. This trend toward the increased use of saline is affirmed in more recent surveys in which 70%–74% of anesthesiologists preferred loss of resistance with saline to that with air.[4,5] Reasons cited for this preference include improved loss of resistance end point, fewer dural punctures, and fewer "patchy" blocks with the saline loss of resistance technique. Those who preferred the air loss of resistance technique did not associate the use of air with increased complications and argued that it improved the ability to identify cerebrospinal liquid in cases of accidental dural puncture.[6] Only 1.9% of anesthesiologists surveyed stated that prior research showed saline to be superior to air.[4,5]

A review of the literature shows a limited number of small studies that suggest that loss of resistance with air is associated with an increased incidence of complications, including difficult catheter insertion, paresthesia, intravascular catheter insertion, accidental dural puncture, postdural puncture headache (PDPH), and partial block.[1,6–14] We conducted a meta-analysis[6,10,11,15–17] to test the hypothesis that loss of resistance with a liquid medium is associated with fewer epidural-related complications.

METHODS

Study Design

We analyzed all identified prospective, randomized, controlled trials (published as full-text journal publications from 1966 to 2008 or as scientific abstracts published after January 2003) that compared the use of the loss of resistance technique with air versus liquid

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mediums (e.g., saline, local anesthetic solution) for identifying the epidural space during epidural anesthesia or analgesia in adults. We thought it reasonable to combine saline and local anesthetic solution within the liquid loss of resistance group on the premise that both are liquids. All pediatric and animal studies were excluded.

Two authors (RS and GP) independently performed the systematic literature search, reviewed each included study for quality, and extracted the relevant data using a standardized data extraction form. A third author (BR) resolved any disagreements. All identified publications were assessed regarding the population cohort (obstetric versus acute [surgical] or chronic pain management) and the following 6 complications associated with the loss of resistance technique: difficult catheter insertion, intravascular catheter insertion, paresthesia, accidental dural puncture, PDPH, and partial block. Varied terminology has been used to describe the inability to produce an appropriate sensory block, including failed, partial, incomplete, spotty, patchy, inadequate, or unsatisfactory block.[8] An unsatisfactory block was defined as incomplete analgesia or no sensory block after adequate dosing at any time after initial placement.[7]

Literature Search Strategy

Relevant keywords were used to design an effective strategy for searching published data. There was no language restriction for trial inclusion; however, no appropriate studies reported in non–English-language journals were identified. When more than 1 publication contained data from a single patient cohort, we included only the publication with the most complete data set. The following electronic databases were searched: Ovid MEDLINE (1966–2008), EMBASE (1974–2008), the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Additionally, abstracts from conferences and scientific meetings of the American Society of Anesthesiologists, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, the European Society of Anaesthesiology, the European Society of Regional Anesthesia, the Australian and New Zealand College of Anesthetists, the Canadian Anesthesiologists Society, the Society of Cardiovascular Anesthesiologists, the International Association for the Study of Pain, and the International Anesthesia Research Society published after January 2003. Further reports were searched within the bibliographies of all identified publications.

Study Quality Assessment

Using a standardized data extraction form, based on The Quality of Reporting of Meta-analyses[18] and The Cochrane Collaboration Guidelines, each study was assessed for quality and then scored (Appendix A) according to the scoring system described by Downs and Black.[19] This scoring system consists of 27 items grouped into 5 categories: reporting (10 items), external validity (3 items), internal validity bias (7 items), internal validity confounding (6 items), and power (1 item). Most items are scored either 0 or 1 according to the criterion specific to each item. One item of reporting is scored as 0, 1, or 2, and the item assessing study power is scored from 0 to 5. The latter, item #27 of the scoring system, evaluated the power of each study by analyzing whether the study had sufficient power to detect a clinically important effect given a significance level of 0.05. To accomplish this, sample sizes were calculated for the comparison of 2 proportions using a 2-sided Fisher's exact test for 6 varying levels of power (70%, 75%, 80%, 85%, 90%, and 95%). Clinical significance was considered to be a difference of 12 percentage points. For each study, the smaller sample sizes of the intervention group were compared with the 6 sample sizes calculated from the 6 values of power. A score of 0–5 was then provided based on the interval where the study sample size lay in relation to the computed sample sizes.

The quality score of each study was then evaluated according to the sum of the scores for all 27 items, with a maximum total of 32 points. Quality was defined as low (total score <10), moderate (total score 10–19), or high (total score >20). Only studies of moderate or high quality were included in the meta-analysis. Three investigators (JA, RS, and BR) scored the studies independently. When there was discordance among the quality scores reported by the 3 investigators, the lowest score was used.

Statistical Analysis

All statistical analyses were performed using Stata software (Version 10, Stata Corporation, College Station, TX). Stata was used to calculate the pooled risk difference estimates and 95% confidence intervals were specified by a random effects model using the method of DerSimonian and Laird (D + L).[20] Cochran's Q-test was used to test the null hypothesis of no significant heterogeneity across studies.[21] The Cochran's Q-statistic follows a χ^2 distribution with $(k - 1)$ degrees of freedom where k is the number of studies. I^2 or the percentage of variation in the measures of association across studies due to heterogeneity was also calculated. I^2 is the equivalent to the quantity of Cochran's Q minus its degrees of freedom divided by Cochran's Q, or $I^2 = (Q - df)/Q$. The value of I^2 ranges between 0% and 100%, where 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity.[22]

Several studies with no events of interest were present in this meta-analysis. For this reason, risk difference estimates were produced leaving behind the need for excluding studies when zero events occur. The risk difference was used to compare the proportion of complications between liquid and air as the medium used during the loss of resistance technique. Pooled D + L risk difference estimates resulting from a random effects model along with their corresponding 95% confidence interval were displayed so that a risk difference less than zero favored the loss of resistance technique with liquid medium over that with air. To derive pooled estimates, the D + L

method calculates weights by taking the inverse of a combination of within-study and between-study variability, which provides a larger variance compared with the variance produced from fixed effects analyses and thus wider confidence intervals.[20]

In accordance with Bradburn et al.,[23] who provide evidence via simulation studies to show that the D + L method has a tendency to underestimate risk differences when event rates are low, pooled risk differences using the method of Mantel-Hanzel (MH) were also computed. The MH method uses a fixed effects model that potentially provided unbiased estimates for low event rates; however, the MH risk differences were not reported because they coincided almost exactly with those of the D + L method and would not have had an impact on our conclusions.

RESULTS

More than 700,000 abstracts were retrieved from the screened databases (Fig. 1). After critical appraisal, 670 records were selected for further evaluation; of those, 15 published prospective, randomized studies investigated the risk of complications associated with air versus liquid medium during the loss of resistance technique. Ten of the selected 15 publications were excluded. These studies and the reasons for exclusion are summarized in Appendix B.

Five publications[6,10,11,15,16] were included in the meta-analysis: 4 studies evaluated the use of labor analgesia via epidural catheter[6,10,11,16] and 1 study involved epidural analgesia without catheter placement for chronic pain management[15] (Tables 1 and 2). The quality assessment scores (range, 16–26) for these studies are detailed in Appendix A. Four[6,11,15,16] of the 5 studies used saline, and 1 study[10] used lidocaine for the liquid medium and compared this with air during the loss of resistance technique. The results are displayed in Tables 3 (obstetric) and 4 (nonobstetric).

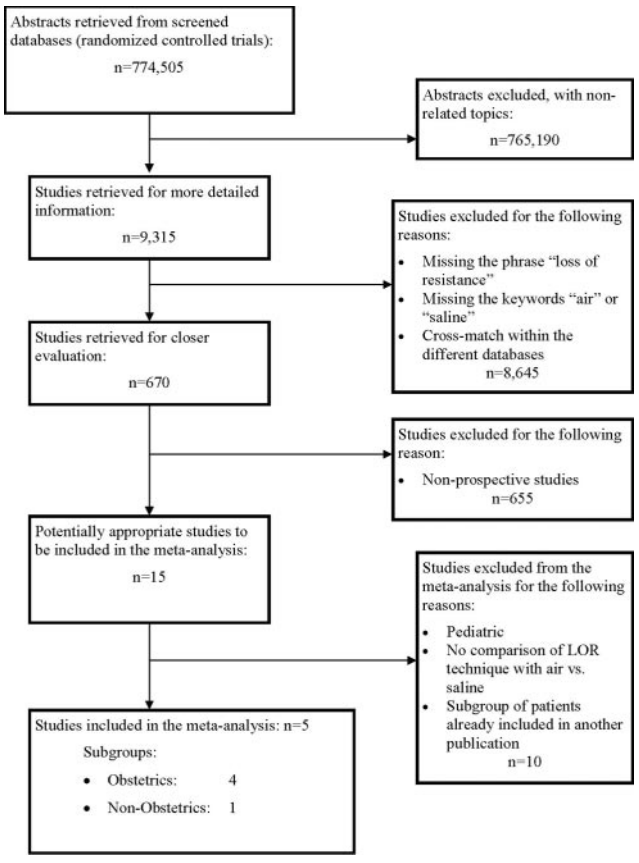

Figure 1. Flow diagram of the systematic literature search.

Difficult Catheter Insertion

The search strategy identified 7 studies[10,11,16,17,24–25] (6 articles and 1 scientific abstract) that investigated the risk of difficult catheter insertion during the loss of resistance technique with air versus liquid medium. Of these, 3 prospective, randomized trials were eligible for inclusion in the meta-analysis.[10,11,16]

Obstetric Studies

Three prospective, randomized studies investigated the risk of difficult catheter insertion during the loss of resistance technique with air versus liquid medium.[10,11,16] There were no significant differences between mediums.

Nonobstetric Studies

No prospective, randomized trials were identified for the acute (surgical) or chronic pain management populations.

Intravascular Catheter Insertion

The search strategy identified 9 studies[6,10,11,16,24,26–28] (8 articles and 1 scientific abstract) that investigated the incidence of intravascular catheter insertion during the loss of resistance technique with air or liquid. Of these, 4 prospective, randomized studies were eligible for inclusion in the meta-analysis.[6,10,11,16]

Obstetric Studies

Four prospective, randomized studies investigated the risk of intravascular catheter insertion during the loss of resistance technique with air versus liquid medium.[6,10,11,16] There were no significant differences between mediums.

Nonobstetric Studies

No prospective, randomized trials were identified for the acute (surgical) or chronic pain management populations.

Paresthesia

The search strategy identified 5 studies[10,11,16,26] (4 articles and 1 scientific abstract) that investigated the incidence of paresthesia associated with epidural placement. Of these, 3 prospective, randomized trials were eligible for inclusion in the meta-analysis.[10,11,16]

Obstetric Studies

Three prospective, randomized studies investigated the risk of intravascular catheter insertion during the loss of resistance technique with air versus

Table 1. Characteristics of Studies Included in the Meta-analysis

Citation	Study design	Patients (*n*)	Location of epidural	Patient population	Measured outcomes	Statistical analysis	Study quality assessment[19]
Obstetric studies							
Evron et al.[10]	Prospective, randomized	365	Lumbar	Obstetric	Incidence of difficult epidural catheter insertion, intravascular catheter insertion, ADP, PDPH, pneumocephalus, partial block, and paresthesia	Kolmogorov-Smirnov test, Mann–Whitney *U*-test, median test, Fisher's exact probability test	26
Beilin et al.[16]	Prospective, randomized	160	Lumbar	Obstetric	Incidence of difficult epidural catheter insertion, intravascular catheter insertion, ADP, partial block*, and paresthesia	χ^2 test, Wilcoxon's ranked sum test	18
Valentine et al.[6]	Prospective, randomized	50	Lumbar	Obstetric	Incidence of intravascular catheter insertion, ADP, and partial block*	χ^2 test with Yates' correction	16
Sarna et al.[11]	Prospective, randomized	67	Lumbar	Obstetric	Incidence of difficult/intravascular catheter insertion, ADP, partial block*, and paresthesia	χ^2 test	19
Nonobstetric study							
Aida et al.[15]	Prospective, randomized	3730	Predominantly lumbar; also cervical and thoracic	Acute or chronic pain	Incidence of ADP, PDPH, and pneumocephalus	Fisher's exact probability test, Mann–Whitney *U*-test	21

ADP = accidental dural puncture; PDPH = postdural puncture headache.

Table 2. Definitions of Partial Block and Stage in Labor for Obstetric Studies

Studies	Study end point	Definition of partial block	Stage in labor
Sarna et al.[11]	Incidence of unblocked dermatomal segments	Not specified	Not mentioned
Valentine et al.[6]	Incidence of unblocked dermatomal segments	Dermatomal segment sensitive to pinprick while adjacent segments above and below are pain free	Early labor
Beilin et al.[16]	Incidence of complete and incomplete block	Complete failed block: no areas of sensory block Incomplete block: missed segments of analgesia	Labor (contractions more than once every 5 min)
Evron et al.[10]	Incidence of unblocked dermatomal segments	Not specified	Labor: cervical dilation at epidural catheter insertion: air = 4 cm; lidocaine = 3.5 cm; air + lidocaine = 3.5 cm

liquid medium.[10,11,16] There were no significant differences between mediums.

Nonobstetric Studies

No prospective, randomized trials were identified for the acute (surgical) or chronic pain management populations.

Accidental Dural Puncture

The search strategy identified 10 studies[6,10,11,15,16,24,26,29,30] (9 articles and 1 scientific abstract) that investigated the risk of accidental dural puncture with loss of resistance technique using either liquid or air. Of these, 5 prospective, randomized studies were eligible for inclusion in the meta-analysis.[6,10,11,15,16]

Obstetric Studies

Four prospective, randomized studies investigated the risk of accidental dural puncture during the loss of resistance technique with air versus liquid medium.[6,10,11,16] There were no significant differences between mediums.

Nonobstetric Studies

One large (n = 3730), prospective, randomized trial of epidurals for chronic pain management investigated accidental dural puncture.[17] There were no significant differences between mediums.

Postdural Puncture Headache

The search strategy identified 4 published studies[10,15,17,30] that analyzed the risk of PDPH after epidural analgesia using the loss of resistance technique with air versus liquid. Two studies were included in the analysis: 1 with obstetric and 1 with pain management patients.[10,15]

Obstetric Studies

One prospective, randomized study investigated the risk of PDPH during the loss of resistance technique

Table 3. Risk Difference and Random Effects Model for Obstetric Patients

	Complications/no. of treated with fluid medium	Complications/no. treated with air	RD (95% CI) (RD <0 favors fluid medium)	D + L pooled RD[a]	
				Combined RD (random effects)	Weights (%)
Difficult catheter insertion					
Evron et al.[10]	7/185	29/180	−0.12 (−0.18 to −0.63)		38.16
Beilin et al.[16]	2/80	2/80	0.00 (−0.05 to 0.05)		39.81
Sarna et al.[11]	5/35	4/32	0.02 (−0.14 to 0.18)		22.03
Total	14/300	35/292		−0.04 (−0.15 to 0.07)	
			Cochran's *Q* test *P* value	0.002	
			I^2	84.3%	
Intravascular catheter insertion					
Evron et al.[10]	11/185	30/180	−0.11 (−0.17 to −0.04)		29.14
Beilin et al.[16]	6/78	4/78	0.026 (−0.05 to 0.10)		26.51
Valentine et al.[6]	0/25	0/25	0.00 (−0.08 to 0.08)		26.95
Sarna et al.[11]	2/35	3/32	−0.04 (−0.16 to 0.09)		17.41
Total	19/323	37/315		−0.03 (−0.10 to 0.04)	
			Cochran's *Q* test *P* value	0.025	
			I^2	67.9%	
Paresthesia					
Evron et al.[10]	3/185	3/180	0.00 (−0.03 to 0.03)		57.99
Beilin et al.[16]	40/78	33/78	0.09 (−0.07 to 0.25)		25.64
Sarna et al.[11]	20/35	18/32	0.01 (−0.23 to 0.25)		15.36
Total	63/298	54/290		0.03 (−0.08 to 0.13)	
			Cochran's *Q* test *P* value	0.122	
			I^2	52.5%	
ADP					
Evron et al.[10]	0/185	3/180	−0.02 (−0.04 to 0.01)		50.66
Beilin et al.[16]	0/78	0/78	0.00 (−0.02 to 0.02)		37.92
Valentine et al.[6]	0/25	0/25	0.00 (−0.08 to 0.08)		4.16
Sarna et al.[11]	0/35	0/32	0.00 (−0.06 to 0.06)		7.25
Total	0/323	3/315		−0.01 (−0.02 to 0.01)	
			Cochran's *Q* test *P* value	0.760	
			I^2	0.0%	
PDPH					
Evron et al.[10]	0/185	1/180	−0.01 (−0.02 to 0.01)	–	–
Partial block					
Evron et al.[10]	6/185	12/180	−0.03 (−0.08 to 0.10)		34.88
Beilin et al.[16]	14/72	27/74	−0.17 (−0.31 to −0.03)		22.08
Valentine et al.[6]	2/25	8/25	−0.24 (−0.45 to −0.03)		14.87
Sarna et al.[11]	2/35	1/32	0.03 (−0.08 to 0.01)		28.17
Total	24/317	48/311		−0.08 (−0.18 to 0.03)	
			Cochran's *Q* test *P* value	0.009	
			I^2	74.0%	

ADP = accidental dural puncture; PDPH = postdural puncture headache; RD = risk difference; CI = confidence interval.

[a] DerSimonian-Laird (D + L) random effects model.

Table 4. Risk Difference and Random Effects Model for Nonobstetric Patients

	Complications/no. of treated with fluid medium	Complications/no. treated with air	RD (95% CI) (RD <0 favors fluid medium)	D + L pooled RD[a]	
				Combined RD (random effects)	Weights
ADP					
Aida et al.[15]	51/1918	48/1812	0.00 (−0.01 to 0.01)	–	–
PDPH					
Aida et al.[15]	5/1918	32/1812	−0.015 (−0.022 to −0.008)[b]	–	–

ADP = accidental dural puncture; PDPH = postdural puncture headache; RD = risk difference; CI = confidence interval.

[a] DerSimonian-Laird (D + L) random effects model.

[b] $P < 0.01$ based on a Fisher's exact test; exact 95% confidence interval reported.

with air versus liquid medium.[10] There were no significant differences between mediums.

Nonobstetric Studies

One large ($n = 3730$), prospective, randomized trial of epidurals for chronic pain management investigated PDPH.[17] Analyzing the risk difference for PDPH, the risk of PDPH was 1.5 percentage points lower (risk difference = −0.015; 95% CI −0.022 to −0.008; $P < 0.001$; Table 3) with liquid than with air during loss of resistance. Because only 1 study was used, the 95% confidence interval for the risk difference using exact methods was provided along with its corresponding P value from Fisher's exact test.

Partial Block

The search strategy identified 9 studies[6,10,11,16,17,25,30,31] (8 articles and 1 scientific abstract) that investigated the incidence of partial block during epidural analgesia. Four of these studies,[6,10,11,16] all with obstetric patients, met inclusion criteria for the meta-analysis.

Obstetric Studies

Four prospective, randomized studies investigated the risk of partial block during the loss of resistance technique with air versus liquid medium.[6,10,11,16] There were no significant differences between mediums.

Nonobstetric Studies

No prospective, randomized trials were identified for the acute (surgical) or chronic pain management populations.

DISCUSSION

This meta-analysis, by including the subsequent study by Evron et al.,[10] in which epidural catheters were inserted by experienced obstetric anesthesiologists and currently contributes more than 50% of the prospectively studied obstetric population, expands on a previous review by Shenouda and Cunningham.[1] This meta-analysis is further strengthened by restricting inclusion to prospective, randomized trials only and contrasts with the review by Shenouda and Cunningham.

This meta-analysis of 4422 patients suggests, despite heterogeneity across studies and the relatively low occurrence of complication events, that liquid (typically saline) as the medium for the loss of resistance technique may potentially reduce the incidence of certain epidural-related complications. Specifically, the risk of PDPH was 1.5 percentage points lower in chronic pain patients. However, this meta-analysis failed to show that loss of resistance medium significantly affected epidural-related complications in obstetric patients. Although loss of resistance medium may be a factor in the development of accidental dural puncture and PDPH,[32–39] our data likely reflect on the role of multiple other factors, including difficult puncture, repeated attempts, needle size, needle rotation, volume of air injected, etc.[38,40] Similarly, although some authors hypothesize that air with loss of resistance causes bubble formation, which leads to a heterogeneous and incomplete distribution of the local anesthetic,[41] this meta-analysis failed to demonstrate a significant difference in incidence of partial block.

Limitations of the meta-analysis include the fact that the definitions of study end points or techniques used were not uniform or clearly defined across the various studies; for example, in the study by Aida et al.,[15] epidural catheters were not placed. This deteriorates the study end point because it omits difficulties with catheter placement and the consequent complications. Furthermore, important clinically relevant rare events, often described in case reports (e.g., symptomatic nerve root compression),[42] which may be related to different loss of resistance techniques, might not be observed in randomized trials and thus not conveyed in meta-analyses. Importantly, there are insufficient data within the included studies to objectively evaluate the effect of loss of resistance medium on factors that have a strong impact on patient satisfaction, including the quality of analgesia (quality of pain relief, onset and distribution of local anesthetic action) or in terms of persistence/appearance of partial block later in the course of labor. Although blinding the patient and outcome assessor was possible, blinding the proceduralist to the specific loss of resistance technique used was not done in the studies included in the meta-analysis. However, it is unlikely that lack of blinding affected the internal validity of these studies. Similarly, we were unable to adjust for "house bias," that is, the preferred technique or the technique with which the investigator had the most experience outside of the study. Additionally, although some of the investigated complications were defined and recorded in a standardized manner, some of the studies did not include all of the study end points.

Limitations of the meta-analytic technique include the fact that pooled estimates may be dominated by 1 study with large numbers (although attempts were made to adjust the weighting of individual studies) and the necessity to use a statistical technique that accommodated the overall low event rate, with some studies reporting zero events.[22]

In summary, this meta-analysis reveals that loss of resistance technique with liquid (versus air) reduces the incidence of PDPH in chronic pain patients. Although these findings may guide clinical practice as to the best method for identifying the epidural space, it is important that cautious interpretation and extrapolation of these findings occur across various patient populations (obstetric, acute [surgical] versus chronic pain management), across epidural placement sites (lumbar versus thoracic versus cervical), and for different stages of labor.

APPENDIX A. Assessment of the Methodological Quality[21]

	Obstetric studies				Nonobstetric study
	Evron[10]	Beilin[16]	Valentine[6]	Sarna[11]	Aida[15]
Reporting					
1. Is the hypothesis/aim/objective of the study clearly described? (yes/no = 1/0)	1	1	0	1	0
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? (yes/no = 1/0)	1	1	1	1	1
3. Are the characteristics of the patients included in the study clearly described? (yes/no = 1/0)	1	1	1	1	1
4. Are the interventions of interest clearly described? (yes/no = 1/0)	1	1	1	1	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? (yes/partially/no = 2/1/0)	1	1	1	1	1
6. Are the main findings of the study clearly described? (yes/no = 1/0)	1	1	1	1	1
7. Does the study provide estimates of the random variability in the data for the main outcomes? (yes/no = 1/0)	1	1	1	0	0
8. Have all important adverse events that may be a consequence of the intervention been reported? (yes/no = 1/0)	1	1	1	1	1
9. Have the characteristics of patients lost to follow-up been described? (yes/no = 1/0)	1	1	0	0	0
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? (yes/no = 1/0)	1	0	0	0	0
External validity					
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
13. Were the staff, locations, and facilities where the patients were treated representative of the treatment the majority of patients receive? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
Internal validity—bias					
14. Was an attempt made to blind study subjects to the intervention they received? (yes/no/unable to determine = 1/0/0)	0	0	0	0	1
15. Was an attempt made to blind those measuring the main outcomes of the intervention? (yes/no/unable to determine = 1/0/0)	1	0	1	0	1
16. If any of the results of the study were based on "data dredging," was this made clear? (yes/no/unable to determine = 1/0/0)	0	0	0	0	0
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? (yes/no/unable to determine = 1/0/0)	0	0	0	0	0
18. Were the statistical tests used to assess the main outcomes appropriate? (yes/no/unable to determine = 1/0/0)	1	1	1	0	1
19. Was compliance with the intervention/s reliable? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
20. Were the main outcome measures used accurate (valid and reliable)? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1

(*Continued*)

APPENDIX A. Continued

	Obstetric studies				Nonobstetric study
	Evron[10]	Beilin[16]	Valentine[6]	Sarna[11]	Aida[15]
Internal validity—confounding (selection bias)					
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
22. Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
23. Were study subjects randomized to intervention groups? (yes/no/unable to determine = 1/0/0)	1	1	1	1	1
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? (yes/no/unable to determine = 1/0/0)	0	0	0	0	1
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (yes/no/unable to determine = 1/0/0)	0	0	0	0	0
26. Were losses of patients to follow-up taken into account? (yes/no/unable to determine = 1/0/0)	1	0	0	1	0
Power					
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	5	0	5	0	0
A = <n1 = 0					
B = n1 − n2 = 1					
C = n3 − n4 = 2					
D = n5 − n6 = 3					
E = n7 − n8 = 4					
F = n8+ = 5					
Total points	26	18	21	16	19

APPENDIX B. Summary of Excluded Studies

Citation	Type of intervention	Number of patients	Measured outcomes	Reason for exclusion
Obstetric studies				
Norman et al.[17]	Obstetric	50	Incidence of difficult epidural catheter insertion, PDPH, and partial block	No comparison of LOR technique with air versus saline: test dose preceded catheter insertion
Beilin et al.[16]	Labor	160	Incidence of difficult catheter insertion, intravascular catheters, ADP, partial block, and paresthesia	Subgroup of patients already included in another publication by Beilin[22]
Leighton and Gross[28]	Labor	33	Detection of intravenously located epidural catheters	No comparison of LOR technique with air versus saline
Philip[26]	Obstetric	32	Incidence of paresthesia, blood vessel puncture, and dural puncture after injection of air into the epidural space	No comparison of LOR technique with air versus saline
Verniquet[27]	Obstetric/labor	202	Incidence of vessel puncture	No comparison of LOR technique with air versus saline

(*Continued*)

APPENDIX B. Continued

Citation	Type of intervention	Number of patients	Measured outcomes	Reason for exclusion
Nonobstetric studies				
Talwar et al.[25]	Inguinal herniotomy	60	Ease of needle placement and successful block	Pediatric study
Lin et al.[29]	Urology surgery	20	Incidence of accidental dural puncture using a 'Membrane in Syringe' technique for the identification of the epidural space	No comparison of LOR technique with air versus saline
Roelants et al.[24]	Abdominal surgery, urological surgery, orthopedic procedures, and other indications	400	Ease of needle placement, incidence of accidental dural puncture, difficult epidural catheter insertion, and intravascular catheters	Pediatric study
Iwama[31]	Elective surgery (not further described)	30	Quality of pain relief, analgesic distribution, etc. depending on volume of saline injected with LOR technique	No comparison of LOR technique with air versus saline
Combined obstetric and nonobstetric study				
Candido and Winnie[30]	Surgery, obstetric, and pain control	20	Onset of anesthesia, analgesic distribution, incidence of PDPH using a 'Dual-chambered Syringe' technique with air and liquid for epidural space identification	No comparison of LOR technique with air versus saline

ADP = accidental dural puncture; PDPH = postdural puncture headache; LOR = loss of resistance.

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