Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Subarachnoid and epidural dexmedetomidine for the prevention of post-anesthetic shivering: a meta-analysis and systematic review

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Background: Post-anesthetic shivering incurs discomfort to patients or even exacerbates their condition. However, no ideal drug has been well established for preventing post-anesthetic shivering. Currently, subarachnoid and epidural dexmedetomidine have demonstrated to have an anti-shivering effect.

Methods: An electronic search was conducted to identify randomized placebo-controlled trials reporting shivering and then compared subarachnoid and epidural dexmedetomidine with placebo in adults undergoing selective surgery. Data assessment and pooling were analyzed by Review Manager 5.3, STATA 15.0 and GRADE-pro 3.6 software.

Results: Twenty-two studies (1389 patients) were subjected to this meta-analysis. The incidence of post-anesthetic shivering decreased from 20.10% in the placebo group to 10.30% in the dexmedetomidine group (RR, 0.48; 95% CI, 0.39–0.59; Z=6.86, P<0.00001, I^2=32%). Non-Indian, epidural-space route and cesarean subgroups indicated a better anti-shivering effect. In the subarachnoid-space route subgroup, a dosage of >5 μg showed significantly superior anti-shivering effects than that of ≤5 μg. Subarachnoid and epidural dexmedetomidine increased the incidence of bradycardia, had no impact on nausea and vomiting, shortened the onset of block and lengthened the duration of block and analgesia. However, its effect on hypotension and sedation remained uncertain. The overall risk of bias was relatively low. The level of evidence was high, and the recommendation of voting results was strong.

Conclusion: Dexmedetomidine as a subarachnoid and epidural adjunct drug could decrease the incidence of post-anesthetic shivering in a dose-dependent manner. However, caution should be taken in patients with original bradycardia.

Keywords: dexmedetomidine, shivering, meta-analysis, subarachnoid, epidural

Introduction

Post-anesthetic shivering (PAS), characterized by spontaneous skeletal muscular tremors due to cutaneous arteriovenous shunt vasoconstriction, has an incidence of about 53%.[1] PAS initiates a hypothermia–hypermetabolism vicious cycle by further facilitating pain and wound infection and prolonging the length of hospitalization.[2] Predisposed factors, including hypothermia, hypovolemia, blood loss, older age, female sex, and the level of anesthesia, can all promote PAS.[3–5]

Although electromyography is sensitive in detecting PAS, but it is cumbersome and therefore not widely used. The Bedside Shivering Assessment Scale (BSAS) is

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used based on skeletal muscular tremors; however, it is rarely used during the perioperative period.[6] Still, there is no currently available objective multidimensional index to detect or predict the occurrence of PAS. Keeping warm and pharmacological intervention are known as two major strategies against shivering, but some recent meta-analyses have shown that extra thermal insulation, including forced air and fluid warming, has no significant effect on PAS.[7,8] Drugs such as meperidine are not recommended as a routine practice, owing to their serious adverse effects, unless the condition becomes uncontrollable. Therefore, a safer and more-effective drug for PAS is urgently required.

Dexmedetomidine (DEX) is a highly selective α-2 receptor agonist used to reduce the shivering threshold and has proven to have a better anti-shivering effect than meperidine.[9–11] A meta-analysis by Hoffman et al.[12] revealed that intravenous (IV) DEX was not an optimal choice against PAS because of cardiovascular adverse effects. Studies proving the safety of subarachnoid and epidural (S&E) DEX have been reported in the USA and Japan.[13–15] The advantages of S&E DEX include prolonged analgesia and deepened sedation with tolerable adverse effects. Recently, some meta-analyses have indicated that S&E DEX reduces the incidence of PAS;[16,17] however, these meta-analyses enrolled non-randomized controlled trials (non-RCTs) and have confounding factors in intervention. Thus, it is difficult to explore whether S&E DEX is propitious against PAS.

The chief goal of this meta-analysis was to assess the anti-shivering effect of prophylactic S&E DEX versus placebo on PAS in patients undergoing selective operation with S&E anesthesia. A supplemental objective of this study was to identify the side effects of prophylactic S&E DEX.

Methods

This manuscript adheres to the applicable PRISMA statements. A protocol can be found at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053006.

Eligibility criteria

Included criteria were: (1) RCTs; (2) adults older than 18 years who were categorized as ASA I–III and underwent selective surgery under spinal anesthesia, epidural anesthesia or combined spinal–epidural anesthesia; (3) DEX was administered via subarachnoid space route (SSR) or epidural space route (ESR); (4) only saline was used as the placebo in the control group and (5) binary data on shivering were available or the available data could be transferred into binary data. Excluded were: use of serotonin receptor agonists, central analgesics, opioids or opioid derivatives; outpatient surgery within 2 hrs; patient with neuromuscular disease, hypothalamus or spinal injury or contraindication to DEX or S&E anesthesia; incomplete reports; and an incorrect statistical approach.

Electronic search

Studies listed in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were retrieved through a pilot search. The final search was run from inception to December 2017 without any restrictions. PubMed search strategies were "shivering"; "shiveringMeSH Terms"; "shiver*"; "chill"; "chill*"; and "dexmedetomidineMeSH Terms"; or "dexmedetomidine"; and "spinal"; "epidural"; "intrathecal" or "intravertebral". Bibliographies from relative articles were checked. Authors were contacted for further information if necessary.

Study selection

Titles and abstracts of all retrieved articles were screened first, and full-text screening was performed in the remaining articles for inclusion by two reviewers (Y.-Z.L. and H.-L.) independently. Discrepancies were settled through discussion.

Risk of bias and quality of evidence

Pilot risk of bias assessment and evidence assessment were first performed on two studies until consensus was reached. Risk of bias was formally assessed by two reviewers (Y.-Z.L. and Y.-J.) independently using the Cochrane Collaboration Risk of Bias tool according to 7 elements and was classified as "low," "high," or "unclear." Evidence quality was assessed using GRADE-pro software, version 3.6, according to 5 elements and was classified as "high," "moderate," "low," or "very low." Strength of evidence recommendation was assessed according to 4 elements and was classified as "strong" or "weak." Evidence quality and recommendation were performed by two reviewers (Y.-Z.L. and H.-L.). Disagreements were resolved through discussion.

Data items

Basic information from the included studies was extracted. The presence of shivering as the primary outcome was defined as any visible skeletal muscle tremors. If there was no clear definition of PAS, dichotomous data were

extracted. Secondary outcomes were side effects, sedation and block information. Bradycardia was defined as a heart rate below 50 bpm. Hypotension was defined as a 30% reduction from the baseline of systolic blood pressure (SBP) or SBP <90 mmHg. Any data on nausea and vomiting were directly extracted. Level of sedation greater than calmness and cooperation was considered as the presence of sedation. Time to peak level of sensory block was defined as the time to reach the maximum level. Time to peak level of motor block was defined as the time to reach a score of 3 on the Bromage scale or modified Bromage scale. Duration of sensory block was defined as 2-dermatome regression from the top sensory level. Duration of motor block was defined as the time to fall to a score of 0 on the Bromage scale or modified Bromage scale. Duration of analgesia was defined as the time of the patient request for first analgesic rescue no matter what degree of pain. Other important complications and information from each study were also extracted, if possible.

Statistical analysis

Risk ratio (RR) with 95% confidence interval (CI) was computed for dichotomous data. Standard mean difference (SMD) with 95% CI was computed for continuous data. Groups of more than two participants with a different dosage of IT DEX were combined into one single group. I^2 statistics were calculated to describe the level of heterogeneity, and values of I^2 greater than 50% were regarded as significantly heterogeneous. The fixed-effects model was used to pool study data when I^2 statistics were <20%; otherwise, the random-effects model was used. Sensitivity analysis was conducted by removing the study with the greatest heterogeneity and reanalyzing the remaining studies. Subgroup analysis and meta-regression were conducted if potential features existed in studies, including ethnic origin, drug administration route, surgical category and dosage. A funnel plot was drawn and interpreted by visual inspection. Data analysis was performed by two reviewers (Y.-Z.L. and X.-P. Y.) using Review Manager software, version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark), and STATA, version 15.0 (Stata Corp, College Station, Texas, United States).

Results

Study selection

Of the 231 articles retrieved, 31 required a further full-text screening. Of these, eight were excluded: three for incomplete data on shivering,[18–20] two for non-RCTs,[21,22] one for IV administration of DEX,[23] one for unavailability of the full text[24] and one for conference literature.[25] Authors were contacted for the missing data, but we failed to receive any replies. Finally, 22 studies meeting all eligible criteria were included in our meta-analysis (Figure 1).[26–47]

Study characteristics

Two studies[45,47] reported post-anesthetic shivering on a 4-point shivering scale and 1 study[38] reported on a 3-point scale; the others treated post-anesthetic shivering as a secondary outcome with no clear definition. Studies were performed in India (11),[26–36] China (7),[37–43] Iran (2),[44,45] Nepal (1)[46] and Egypt (1).[47] Surgical categories included Cesarean sections (7),[37,38,40–43,45] lower limb (6),[27,33–36,44] gynecological (4),[33,39,46] urinary (3),[28,31,33] lower abdominal (3)[30,46,47] and others. Injection of DEX was over SSR (14)[27–33,36–41,43–47] and ESR (3).[26,34,35,42] Via SSR, most implementations were at a dosage of ≤5 μg (15)[27–33,36–41,43–47] while others received >5 μg (5).[30,33,41,43,47] Sample sizes ranged from 40 to 100. Individual characteristics of each study are listed in Table 1.

Study risk of bias

Summary of the risk of bias for the 22 studies is considerably low and shown in Figure 2.

Quality of evidence

The quality of evidence was upgraded for a large effect size (RR_{PAS}<0.5) and dose–response gradient. The final evidence level was high. The evidence recommendation was strong for the net benefits (Figure 3).

Primary outcome

Incidence of post-anesthetic shivering

A total of 22 studies with 1389 patients directly reported the number of patients presenting shivering and all data were available to pool. The incidence of post-anesthetic shivering decreased from 20.10% in the control group to 10.30% in the experimental group (RR, 0.48; 95% CI, 0.39–0.59; Z=6.86, P<0.00001, I^2=32%; Figure 4). Sensitivity analysis indicated that after exclusion of the study from Shahi et al.,[34] I^2 decreased from 32% to 8% (RR, 0.47; 95% CI, 0.39–0.55;Z=8.67, P<0.00001). Subgroup analysis showed no significant difference in ethnicity, surgical category or drug administration route

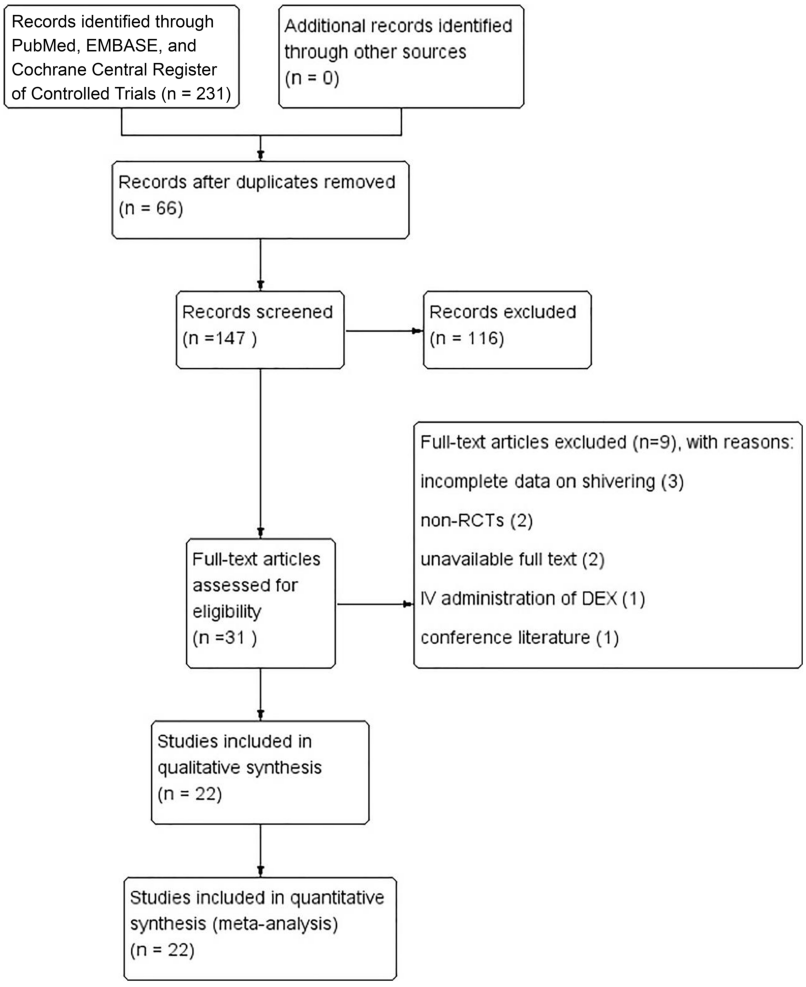

Figure 1 Flow diagram.
Abbreviations: RCTs, randomized controlled trials; IV, intravenous; DEX, dexmedetomidine.

(I^2=0, 0, 16.6%). Non-Indian, SSR and cesarean subgroups (RR, 0.46, 0.44 and 0.44, respectively) showed lower risk ratios than that in the Indian, ESR and non-cesarean subgroups (RR, 0.51, 0.50 and 0.49, respectively; Figure 4). Meta-regression for PAS indicated no significant proportional change in ethnicity, drug administration route or surgical category (Coef, 0.16, −0.44 and−0.20; P=0.72, 0.24 and 0.63, respectively; Figure 5). In the SSR subgroup, a dosage of >5 μg showed a superior anti-shivering effect than that of ≤5 μg (RR, 0.23, 0.60; 95%CI, 0.11–0.49 and 0.40–0.90 respectively; I^2, 78.9%; Figure 4). A funnel plot revealed visual symmetry after excluding the study of Shahi *et al*.[30] (Figure 6). The results indicated that DEX was able to lower PAS with no significant statistical heterogeneity. Ethnicity, drug administration route or surgical category were not the sources of heterogeneity. Non-Indian and SSR groups (especially at a dose of >5 μg) as well as cesarean subgroups showed a better anti-shivering effect. Reporting bias existed in the study of Shahi et al.[34]

Secondary outcome

Bradycardia

A total of 18 studies reported the presence of bradycardia, and data from 12 studies[26,27,30,32,33,36,39,40,44–47] with 797 patients were available to pool. The incidence of bradycardia increased from 5.84% in the control group to 11.13% in the DEX group (RR, 2.49; 95% CI, 1.45–4.28; Z=3.30, P=0.001, I^2, 9%).

Hypotension

A total of 18 studies reported the presence of hypotension, and data from 10 studies[26,27,30,31,33,36,39,40,44,45] with 646 patients were available to pool. The incidence of hypotension increased from 14.89% in the control group to 27.42% in the DEX group (RR, 2.38; 95% CI, 0.76–

Table 1 Characteristics of 22 studies

Study	Size	Ethnicity	Surgery type	Anesthetic regim	Experimental group	Control group	Total volume (ml)	Warming strategy
Kiran 2017[26]	46	India	Infra-umbilical	EA(L2–3)	0.5%ropi 9 mg +10 μg DEX	0.5%ropi 9 mg +NS	18.0	Not warmed
Ashutosh 2017[27]	50	India		SA (L3–4)	0.5%ropi 15 mg +5 μg DEX	0.5%ropi 15 mg +NS	3.1	Not warmed
Chattopadhyay 2017[28]	60	India	TURP	SA (L3–4/4–5)	0.5%bupi 6 mg +3 μg DEX	0.5% bupi 7.5 mg +NS	1.5	Not warmed
Patro 2016[29]	60	India	infra-umbilical	SA (L3–4)	0.5%bupi 15 mg +5 μg DEX	0.5% bupi 15 mg +NS	3.5	Not warmed
Naaz 2016[30]	100	India	Lower abdominal	SA (L3–4)	D1: 0.5% bupi 12.5 mg +5 μg DEX D2: 0.5% bupi 12.5 mg +10 μg DEX D3: 0.5% bupi 12.5 mg +15 μg DEX D4: 0.5% bupi 12.5 mg +20 μg DEX	0.5% bupi 12.5 mg+NS	3.0	Not warmed
Samantaray 2015[31]	40	India	Urological	SA (L3–4/4–5)	0.5% bupi 15 mg +5 μg DEX	0.5% bupi 15 mg +NS	3.5	Not warmed
Nethra 2015[32]	40	India	perianal	SA (L3–4/4–5)	0.5% bupi 6 mg +5 μg DEX	0.5% bupi 6 mg +NS	1.7	Not warmed
Shaikh2014[33]	90	India	urological, gynecological, orthopedic	SA (L3–4)	D1: 0.5% bupi 15 mg +5 μg DEX D2: 0.5% bupi 15 mg +10 μg DEX	0.5% bupi 15 mg +NS	3.5	Not warmed
Shahi2014[34]	80	India	Lower limb	EA(L2–3/3–4)	0.5% bupi 60 mg +0.5 μg/kg DEX	0.5% bupi 60 mg +NS	15.0	Not warmed
Jain2012[35]	60	India	lower-limb, orthopedic	CSEA	0.5% bupi 12.5 mg (SA) +2 μg/kg DEX (EA)	0.5% bupi 12.5 mg (SA)+NS (EA)	12.5	Not warmed
Gupta R 2011[36]	60	India	lower limb	SA (L3–4/4–5)	0.75% ropi 22.5 mg +5 μg DEX	0.75% ropi 22.5+NS	3.5	Not warmed
Bi 2017[37]	60	China	Cesarean section	SA (L2–3/3–4)	D1: 0.5% bupi 10 mg +3 μg DEX D2: 0.5% bupi 10 mg +5 μg DEX	0.5% bupi 10 mg +NS	2.0	Not warmed
He 2017[38a]	90	China	Cesarean section	SA (L3–4)	D1: 0.5% bupi +4 μg DEX D2: 0.5% bupi +8 μg DEX	D1: 0.5% bupi +NS D2: 0.5% bupi +NS	3.0	Not warmed
Qi & L 2016[39]	72	China	hysteroscopy	SA (L2–3)	0.375% ropi 7.5 mg +5 μg DEX	0.375% ropi 7.5 mg +NS	3.0	Not warmed
Qi & C 2016[40]	78	China	Cesarean section	SA (L3–4)	0.5% bupi +5 μg DEX	0.5% bupi +NS	2.0	Not warmed
Li2015[41]	42	China	Cesarean section	SA (L2–3/3–4)	0.25% bupi 10 mg +10 μg	0.25% bupi 10 mg	4.0	Not warmed
Han2014[42]	40	China	Cesarean section	EA (L2–3)	0.75% ropi 112.5 mg +1 μg/kg DEX	0.75% ropi 112.5 mg +NS	17.0	Not warmed
Sun2015[43]	60	China	Cesarean section	SA (L2–3/3–4)	0.5%bupi10 mg +10 μg	0.5%bupi10 mg	3.0	Not warmed
Poupak 2018[44]	60	Iran	lower limb	SA (L4–5)	0.5%bupi 15 mg +5 μg DEX	0.5%bupi 15 mg +NS	3.0	Not warmed
Nasseri 2017[45a]	50	Iran	Cesarean section	SA (L3–4/4–5)	0.5% bupi12.5 mg +5 μg DEX	0.5%bupi12. mg +NS	3.0	OR: 22–26°C
Gautam 2017[46]	71	Nepal	inguinal hernia repair, vaginal hysterectomy	SA (L3–4)	0.5%bupi 12.5 mg +5 μg DEX	0.5% bupi 12.5 mg +NS	3.0	Not warmed
Moawad 2015[47a]	80	Egypt	lower abdominal	SA (L3–4/4–5)	0.5% bupi 7.5 mg +10 μg DEX	0.5% bupi 7.5 mg+NS	3.0	OR: 22–24°C

Note: [a]study with definition of PAS.

Abbreviations: EA, epidural anesthesia; SA, subarachnoid anesthesia; ropi, ropivacaine; bupi, bupivacaine; DEX, dexmedetomidine; NS, normal saline; OR, operation room; TURP, transurethral resection of prostate.

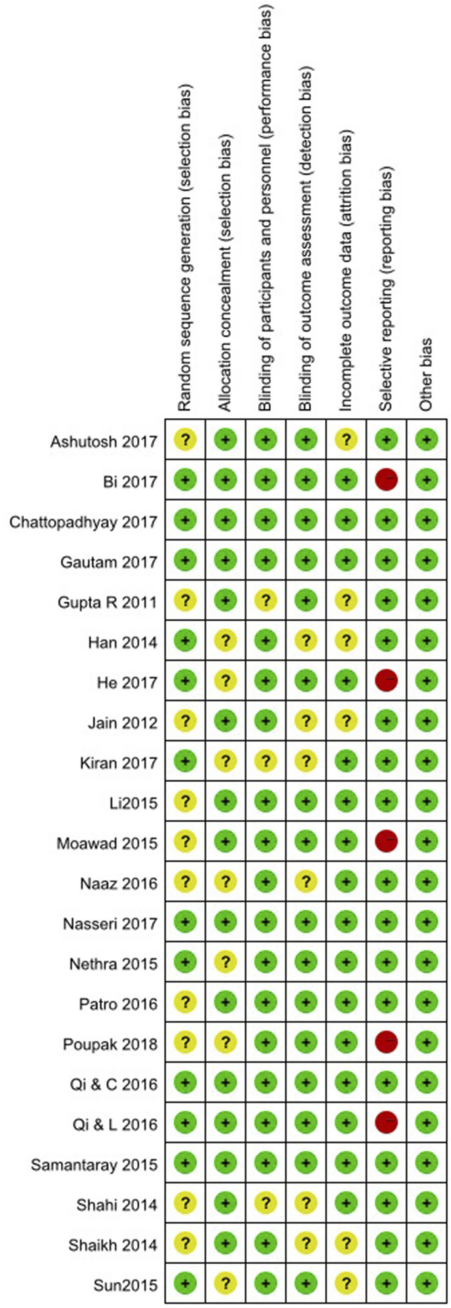

Figure 2 Risk-of-bias summary.
Abbreviations: "+", low risk of bias; "?", unclear risk of bias; "-", high risk of bias.

7.64; Z=1.49, P=0.14, I^2=92%). This result could not indicate that S&E DEX increased the incidence of hypotension and had nostatisticalsignificance with large statistical heterogeneity.

Nausea and vomiting

A total of 19 studies with 1189 patients reported the presence of nausea and vomiting and all were available to pool.[26–39,42,44–47] The incidence of nausea and vomiting decreased from 10.54% in the control group to 7.95% in the DEX group (RR, 0.81; 95% CI, 0.58–1.15; Z=1.18, P=0.24, I^2=0%).This result did not indicated that S&E DEX decreased the incidence of nausea and vomiting.

Onset of sensory block

Data from 11 studies[29,31,36–40,42–44,46] with 691 patients were available to pool. The result showed S&E DEX shortened the time to reach the peak level of sensory block (SMD, −0.72; 95% CI, −1.22–−0.22; Z=2.84, P=0.005, I^2=89%).

Onset of motor block

Data from 6 studies[26,29,33,39,40,44] with 406 patients were available to pool. The result showed S&E DEX shortened the time to reach Bromage3 (SMD, −1.80; 95% CI, −3.15 to −0.45; Z=2.61, P=0.009, I^2=97%).

Duration of sensory block

Data from 8 studies[27–31,36,42,44] with 470 patients were available to pool. The result showed S&E DEX prolonged the time of 2-dermatome regression from the top sensory level (SMD, 3.71; 95% CI, 2.29–5.14; Z=5.11, P<0.00001, I^2=96%).

Duration of motor block

Data from 10 studies[28–30,33,37,39,41,43,44,46] with 675 patients were available to pool. This result showed S&E DEX prolonged the time to fall to a score of 0 on the Bromage scale or modified Bromage scale (SMD, 3.60; 95% CI, 2.22–4.97; Z=5.13, P<0.00001, I^2=98%).

Duration of analgesia

Data from 12 studies[26–30,32,33,36,40,42,44,46] with 711 patients were available to pool. This result showed S&E DEX prolonged the time of the patient request for first analgesic rescue (SMD, 4.43; 95% CI, 3.00–5.86; Z=6.09, P<0.00001, I^2=97%).

Discussion

Our systematic review and meta-analysis provide clear evidence that preventive utilization of S&E DEX attenuates the incidence of PAS. Further evidence indicates S&E DEX has no significant correlation with surgical type, ethnicity or drug administration route. However, via SSR, a dose of >5 μg had a better anti-shivering effect than a dose of ≤5 μg.S&E DEX increases the incidence of bradycardia, has no effect on nausea and vomiting, shortens the onset of sensory/motor block and prolongs the duration of both sensory/motor block and analgesia;

Question: Should IT DEX be used for PAS?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IT DEX	Contriol	Relative (95% CI)	Absolute		
The incidence of PAS												
22	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	79/767 (10.3%)	125/622 (20.1%)	RR 0.48 (0.39 to 0.59)	105 fewer per 1000 (from 82 fewer to 123 fewer)	ΘΘΘΘ HIGH	CRITICAL
								0%		-		

[1] RR(PAS)<0.5

[2] Dosage >5ug has better anti-shivering effect than that of ≤5ug

Figure 3 Quality of evidence.
Abbreviations: IT, intrathecal; DEX, dexmedetomidine; PAS, post-anesthetic shivering.

however, its effect on hypotension remains unknown. The hierarchy of evidence quality for primary outcomes is high, and the strength of recommendation is strong.

The greatest concern regarding the off-label administration route of DEX is its neurotoxicity. However, studies have demonstrated S&E DEX has neither a pathological impact on morphological changes in neural tissue,[48,49] nor histological evidence of neurotoxicity in human beings.[50] As a supplement of local anesthetics, S&E DEX attenuates bupivacaine-induced perineural inflammation[51] and lidocaine-induced cytotoxicity[52] and promotes spinal-cord injury recovery by regulating apoptosis and suppressing inflammation.[53] Furthermore, S&E DEX is safe in infants and young children[54,55] and shows a neuroprotective effect almost equivalent to that of methylprednisolone.[56] Although the use of S&E DEX is supported by strong scientific evidence[57] and studies are emerging on its efficiency and safety, clinicians should be cautious about high cumulative dosages or concentrations,[58,59] as a dosage for 5 μg/kg over ESR[60] may induce neurotoxic effects. In our analysis, S&E DEX is safe to use at 20 μg and 2 μg/kg via SSR and ESR, respectively.

Our meta-analysis has primary pragmatic implications for S&E DEX as it reduces PAS prophylactically. However, one included study in our review by Shahi et al.[34] shows that S&E DEX increased the incidence of PAS (D, 30%; C, 12.5%), which is contrary to the results of the remaining 21 studies. Their study contributes 24% of total heterogeneity and may therefore have reporting bias according to our funnel plot. No study has yet reported that DEX increased PAS. They ascribed this to DEX-induced hypothermia, but Moawad et al.[47] demonstrated that perioperative body temperature is slightly higher for S&E DEX compared to placebo. In the end, we did not exclude their data because no distinct method or clinical heterogeneity was found. Our subgroup analysis and meta-regression could not statistically infer whether ethnicity, drug administration route or surgical category was the source of heterogeneity. We suggested that S&E DEX used in non-Indian patients undergoing cesarean section via ESR might have a better anti-shivering effect, but this needs further exploration because of our small simple size, especially in the ESR group. We did not conduct a meta-regression on dosage because different administration routes existed in the same dosage. In the SSR subgroup, we tried to find a dose-dependent effect by dividing the studies into >5 μg and ≤5 μg dosages. We concluded that S&E DEX in a dosage>5 μg had a better anti-shivering effect than a dosage of ≤5 μg.

We note that meta-analysis from Zhang et al.[61] suggested that S&E DEX reduced the incidence of PAS and was moreeffective with a dose of 5 ug via SSR, especially in cesarean section; this finding partly agreed with our study. However, they included 15studies less than than our meta-analysis as well as enrolled non-randomized controlled trials (non-RCTs), including some studies that had confounding factors in experimental groups, and did not evaluate evidence quality or run a meta-regression. Another meta-analysis from Liu et al.[62] included 5 studies and assured the efficacy of S&E DEX for PAS (which agreed with ours). However, they opposed S&E DEX for the high price and hemodynamic fluctuations. Regardless, DEX has been included in the medical insurance systems of many countries, and its hemodynamic fluctuations have been shown to be tolerable.

Secondary outcomes emerged from our meta-analysis. First, our hemodynamic information was in agreement with that of other meta-analysies.[61,63,64] We confirmed that S&E DEX increases the incidence of bradycardia, but could not suggest that S&E DEX increases the

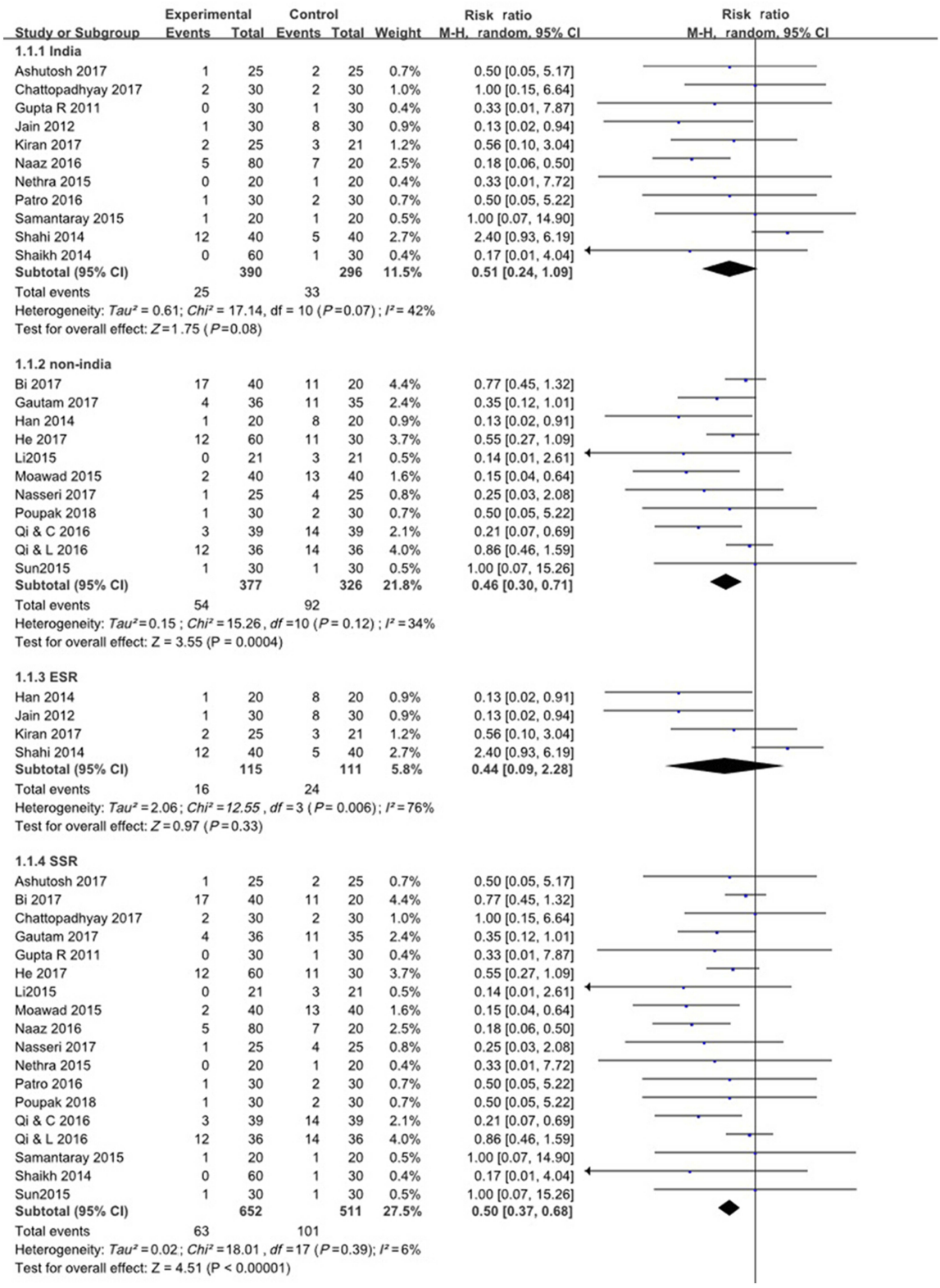

Figure 4 Continued.

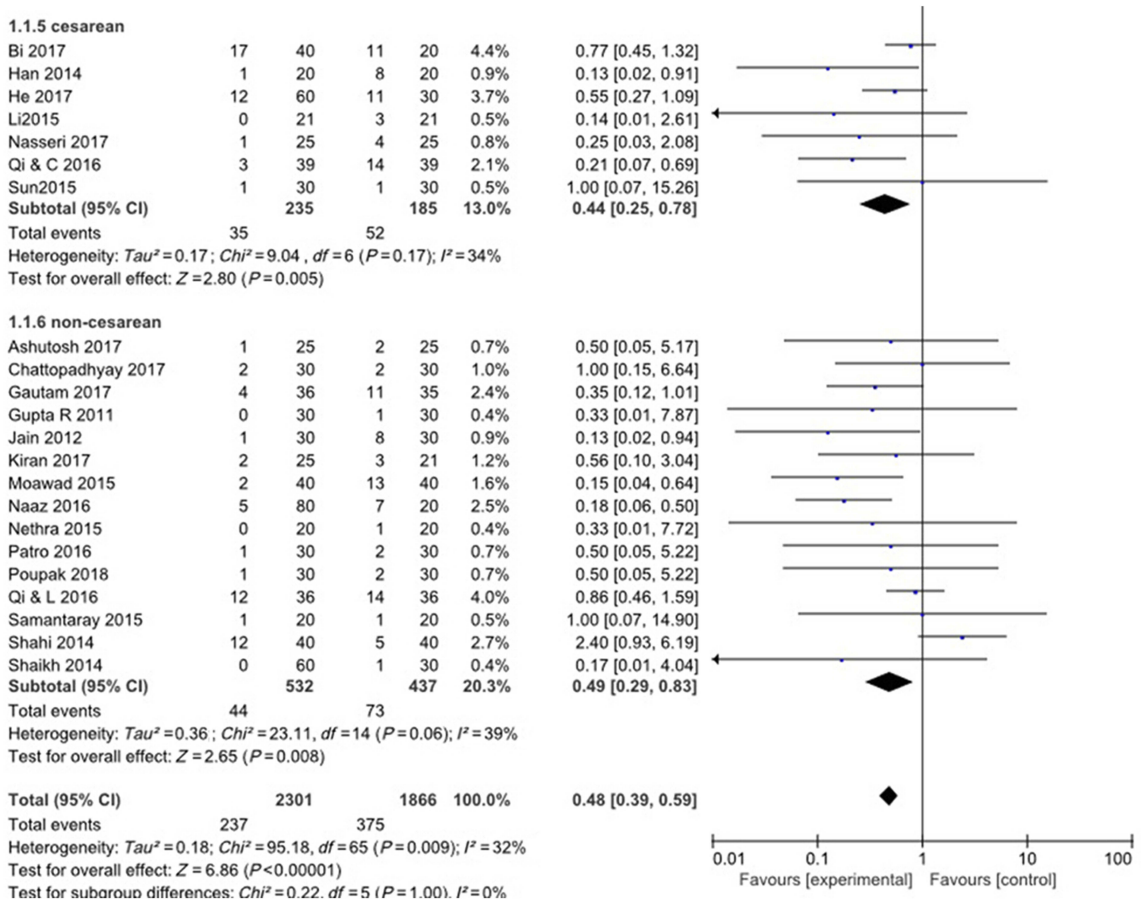

Figure 4 Forest plot for PAS.
Abbreviations: ESR, epidural-space route; SSR, subarachnoid-space route.

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. metareg _ES ethnic route surgery, wsse(_selogEs) bsest (reml)
Iteration 1: tau^2 = 0
Iteration 2: tau^2 = .0548216
Iteration 3: tau^2 = .07810897
Iteration 4: tau^2 = .07919806

Meta-analysis regression                          No of Studies =    20
                                                  tau^2 method       reml
                                                  tau^2 estimate =   .0792

Sucessive values of tau^2 differ by less than 10^-4 :convergence achieved
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ethnic	.2457101	.4663164	0.53	0.598	-.6682533	1.159673
route	-.5111932	.4019835	-1.27	0.203	-1.299066	.27668
surgery	-.2045483	.4173179	-0.49	0.624	-1.022476	.6133797
_cons	1.088097	.5041888	2.16	0.031	.0999047	2.076289

Figure 5 Meta-regression.

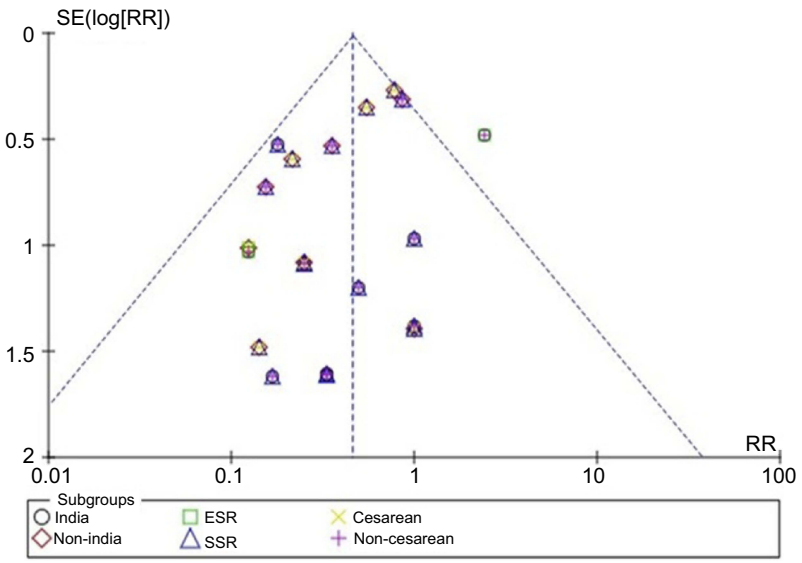

Figure 6 Funnel plot for PAS. Study from Shahi et al falls outside of the funnel plot.

incidence of hypotension because 95%CI of RR stretched across 1 and heterogeneity was tremendous (I^2=92%). Second, we deduced that S&E DEX had no impact on the incidence of nausea and vomiting, which was consistent with other studies.[63] Third, we concluded S&E DEX significantly shortened the onset time of peak block level and prolonged both sensory/motor block and analgesia. Although significant heterogeneity (I^2>95%) exists in these pooled data, the overall effect size was large and meaningful, which was similar to thatfound in previous studies.[65,66] However, these resultsshould be considered from a practical outlook as to whether this prolongation comes at the cost of longer hospital stays and increased patient burdens. We suggest that S&E DEX is not applicable for outpatients undergoing short surgeries (<60 min). Finally, each included study showed that S&E DEX deepened sedation compared with the placebo, which agreed with other studies.[67,68]

Compared with previous studies, our study has unique strengths. First, we introduce strict eligibility by retrieving only RCTs and excluding studies using serotonin receptor agonists, central analgesics, opioids or opioid derivatives in case of their interferential and controversial anti-shivering effects. It is clear that DEX has an anti-shivering effect since no evidence has been revealed otherwise. Moreover, a study by Hocker et al.[69] suggests that meperidine exerts an anti-shivering effect by decreasing the shivering threshold only through an α_{2A}-receptor but not a μ-receptor. A recent meta-analysis by Zhou et al.[70] shows that serotonin receptor antagonist ondansetron has no anti-shivering effect. To obtain the net effect of S&E DEX, we intentionally omitted drugs (fentanyl, butorphanol) from our original eligibility criteria with the controversial auxiliary component to combine with local anesthetics that act as plausible confounding factors. Second, we dismissed doubts over roles of ethnicity, surgical category, and route of drug administration by conducting meta-regression and found no source of heterogeneity. Finally, we graded the quality of evidence and provided recommendations for clinical application.

Our meta-analysis has some limitations. First, all reviewed studies have small sample sizes (20–50 patients/group) and a small number of PAS, which increases the probability of type I error and reporting bias. Second, study from Shahi et al.[34] has the inverse result and considerable reporting bias (asymmetry of funnel plot), but it does not change the overall result, and the level of heterogeneity is acceptable. Third, all included studies report shivering through visual inspection but not instrument detection, and three articles used the shivering scale, which may underestimate the incident of PAS when patients are in a pre-shivering condition such as peripheral vasoconstriction. Fourth, the ethnic concentricity in India and China may limit the generalization of our findings, and therefore studies involving other ethnicities are needed. Fifth, on account of inconsistent sedation scales and different measuring times, most details regarding the number of events at each sedation level in the same endpoint were unavailable for extraction. lastly, the full text from Gangadhara et al.[24] was not available from the authors,

thus, we believe that future meta-analyses can cover this shortage.

Several issues need to be addressed. First, owing to different pharmacodynamics and pharmacokinetics of children to adults, we did not include pediatric studies. Second, few studies report on temperature, which restricted us from distinguishing whether temperature has an effect on PAS.

Conclusion

In this study, we demonstrate that as an adjuvant drug, prophylactic S&E DEX attenuates PAS. Moreover, a dose of >5 μg over SSR has a better anti-shivering effect than a dose of ≤5 μg. However, this is not applicable to mega-doses, high concentrations or outpatients. This conclusion should be interpreted cautiously when patients have an underlying disease such as bradycardia.

Abbreviations

PAS, Post-anesthetic shivering; BSAS, Bedside Shivering Assessment Scale; DEX, Dexmedetomidine; IV, Intravenous; S&E, Subarachnoid and epidural; non-RCTs, Randomized controlled trials; SSR, Subarachnoid-space route; ESR, Epidural-space route; SBP, Systolic blood pressure; RR, Risk ratio; CI, Confidence interval; SMD, Standard mean difference.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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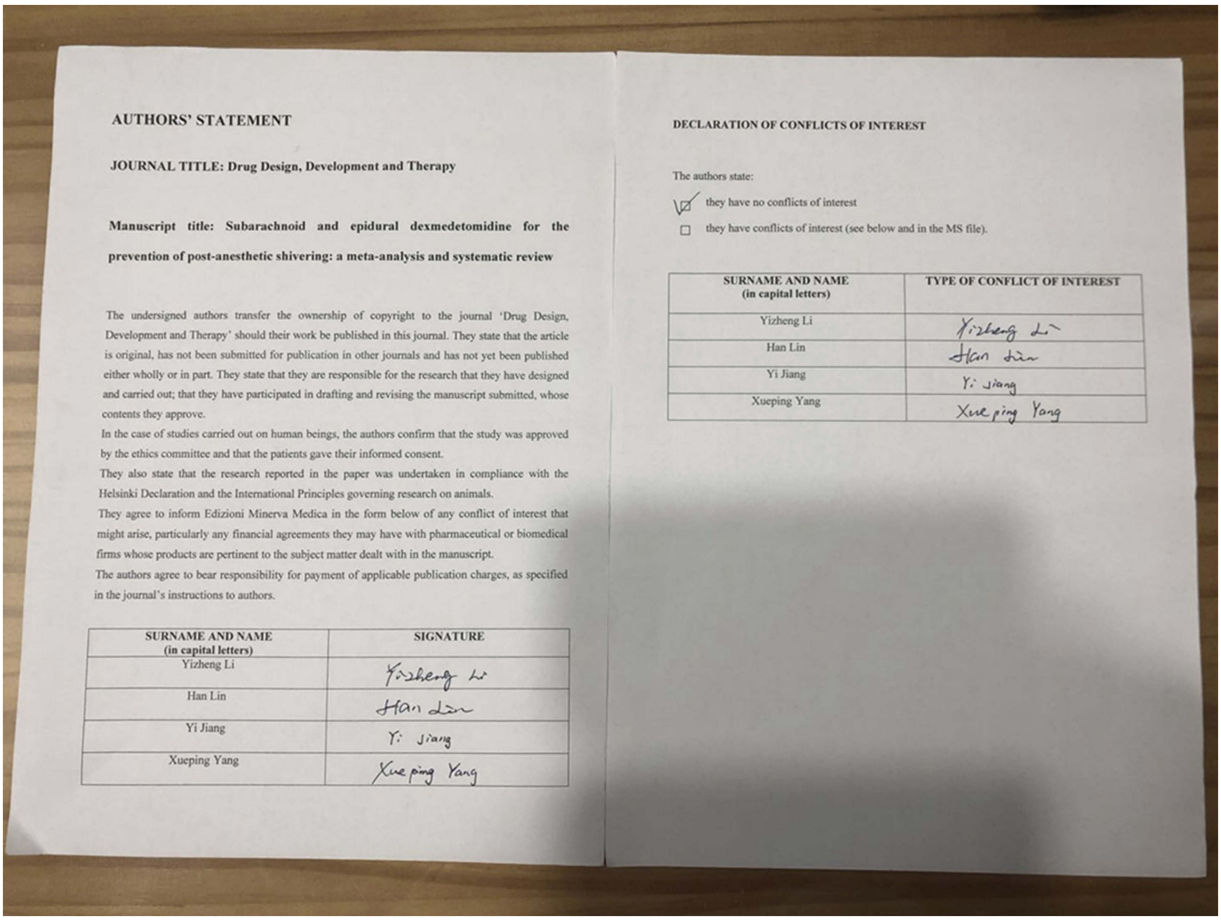
Supplementary material



AUTHORS' STATEMENT

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Manuscript title: Subarachnoid and epidural dexmedetomidine for the prevention of post-anesthetic shivering: a meta-analysis and systematic review

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The authors state:

☑ they have no conflicts of interest

☐ they have conflicts of interest (see below and in the MS file).

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Figure S1 Authors' statement.