Review Article

Efficacy and safety of adjuvant intrathecal dexamethasone during spinal anesthesia: A systematic review and meta-analysis

ABSTRACT

The use of intrathecal (IT) dexamethasone during subarachnoid block (SAB) has not been evaluated. There are no pooled data available to decide on the optimal regimen of IT dexamethasone during SAB, irrespective of the type of surgery. There is uncertainty about its dosage, effectiveness, and safety, and a need to establish clear guidelines on its use. Our objective was to evaluate the effectiveness and safety of use of IT dexamethasone during SAB. We performed a meta-analysis (PROSPERO, CRD42022304944) of trials that included patients who underwent a variety of surgical procedures under SAB. Patients received concomitant IT dexamethasone as an adjuvant to spinal local anesthetics. The analyzed outcomes included sensory and motor effects as well as adverse and/or beneficial side effects. Subgroup analysis was planned based on different doses used. Trial sequential analysis (TSA) was used to estimate the required sample size information (RIS) for each outcome. Eighteen studies (2531 participants) were included in this analysis. Addition of IT dexamethasone (4-8 mg) to heavy bupivacaine effectively prolonged the duration of sensory blockade (mean difference, MD = 63.8 minutes; [95% confidence interval, CI, 33.1-94.5], P < 0.0001), two-segment regression time (MD = 20.1[95% CI, 0.96-39.2], P = 0.04) and first rescue analgesic time (MD = 143.3 [95% CI, 90.3-196.0], P = 0.001). Subgroup analyses revealed superior effects of 8 mg dose over 4 mg for sensory and analgesic effects. The effect of dexamethasone on duration of motor blockade was inconclusive. Additionally, lower risk ratios (RRs) were recorded for spinal anesthesia-related hypotension (RR = 0.74 [95% CI, 0.6-0.9], P = 0.0003) and nausea/vomiting (RR = 0.62 [95% CI, 0.41-0.93], P = 0.02) in the dexamethasone group. For outcomes such as sensory blockade, analgesia, and hypotension, the required information size was reached during TSA. In conclusion, IT dexamethasone, used as an adjuvant to spinal local anesthetic, especially at the dose of 8 mg, increases sensory blockade duration and the time for request of the first rescue analgesic. SAB-induced side effects such as hypotension, nausea, and vomiting are lesser with the use of IT dexamethasone. However, further studies are necessary to draw meaningful conclusions on its safety profile.

Key words: Adjuvants, analgesia, anesthesia, dexamethasone, meta-analysis, spinal

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Introduction

A variety of agents have been used as adjuvants to prolong the effects of local anesthetics during sub-arachnoid block (SAB) *viz.* epinephrine, lipophilic fentanyl, sufentanil, hydrophilic morphine, clonidine, midazolam, ketamine, neostigmine, and magnesium sulfate.[1-4] Addition of corticosteroids like dexamethasone could accentuate the sensory effects, duration as well as quality of peripheral nerve blockade.[5,6] Currently available studies on the intrathecal (IT) use of dexamethasone as an adjuvant include only data from randomized controlled trials (RCTs) and mention a variety of dosage schedules of the drug. There are no pooled data available to decide on the optimal regimen of IT dexamethasone during SAB, irrespective of the type of surgery. Further, the data from the obstetric population remains unclear. There is uncertainty about its dosage, effectiveness, and safety, and a need to establish clear guidelines on its use. The present review was planned to assess the efficacy of dexamethasone as an adjuvant to bupivacaine or other local anesthetics for SAB.

Methods

Registration and protocol

This meta-analysis is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses.[7] The protocol was registered with PROSPERO (CRD42022304944, crd.york.ac.uk).

Eligibility criteria

We selected prospective RCTs with adult patients (>18 years) undergoing all types of surgery under SAB, who received concomitant IT dexamethasone as an adjuvant to local anesthetics such as bupivacaine. We included studies with patients who concomitantly received dexamethasone via routes other than IT and also those where other adjuvants were used intrathecally. Subjects under 18 years of age and those with cardiac illnesses, bleeding disorders or on anticoagulant therapy were excluded. Studies with inconclusive data that could not be clarified after attempts to contact the authors were excluded from this review.

Information sources

An electronic literature search, specifically restricted to RCTs on the use of dexamethasone during SAB was conducted in Medline, Embase, CINAHL (EBSCO host), Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials. The bibliography of the retrieved manuscripts was searched for additional studies pertaining to our primary outcome of interest. Our search dated from inception to the most recent study. Cohorts with matched controls, retrospective studies, reviews with inadequate information on primary outcome interests, abstracts, and letters to the editor were not included. The detailed search strategy is shown in Supplementary Data 1, which depicts the keyword-based search for the inclusion terms.

Study selection and data collection

The eligible manuscripts were assessed, and data were extracted following a standardized format. Studies were collected by TPT and VS. Discrepancies were handled by agreement or by a third author AD. The extracted items comprised the study characteristics, risk of bias domains, participant disposition, and study outcomes. Participants of interest were those who received SAB with IT local anesthetics and undergoing a variety of surgical procedures. The type of surgery included cesarean sections, orthopedic, gynecologic, urological, or any similar. Interventions referred to the IT administration of dexamethasone as an adjuvant to local anesthetics at 2-8 mg dose. The comparison of variables was as follows: study drug compared to control (such as saline) or any other alternative adjuvant used. Comparators included the IT local anesthetic administered control group subjects who received no dexamethasone. Subjects receiving a comparative drug such as dexmedetomidine or an opioid intrathecally as adjuvant were included. Outcomes included efficacy parameters like sensory and motor effects, duration or degree of analgesia, and adverse effects such as hemodynamic consequences. Because we studied the usefulness of adjuvant dexamethasone in the perioperative period following spinal anesthesia, the outcomes such as sensory duration and analgesia time were considered as primary outcomes. The rest of the outcomes such as motor effects, adverse effects etc., were considered secondary.

Study endpoints

The endpoints of this review were (1) onset of sensory block, defined as the time interval between the IT administration of the drug and the T_{12} or higher dermatome sensory effect, (2) duration of sensory block, defined as time to regress to S_1 from the maximum sensory block level, (3) two-segment regression; "two-segment" defined as two dermatome segments from the maximum sensory block level or to achieve T_{10} level, (4) duration of analgesia (pain-free period), defined as the period from the time of IT injection to the time of first complaint of pain or first rescue analgesia, (5) onset of motor block, defined as the time between the IT injection to the modified Bromage score of 1 or higher, (6) duration of motor block, defined as the time of regression to modified Bromage score of 0, and (7) incidence of side effects such as hypotension and bradycardia episodes, nausea, vomiting, shivering, pruritis, respiratory depression and post dural-puncture headache (PDPH).

Data synthesis and analysis of outcomes

Relevant data for the evaluation of the outcome of interest were extracted from each study. The data presented in tables, text, and images were used as the primary sources for extraction. Data were reported as 95% confidence intervals (CI). The median was used to estimate the mean if the value was not reported. Whenever the standard error of the mean (SEM) was reported, the SD was obtained using the formula SD = SEM × √N. We combined the mean and SD groups into single groups by repeating Cochrane's formula whenever necessary.[8,9] Calculatoratoz.com/en/was used to measure the difference between pre- and post-group SD measurements [$\sigma_D = \sqrt{(\sigma_1^2/N_1 + \sigma_2^2/N_2)}$]. If multiple data were provided, then they were converted into pooled statistical averages. If the exact time point was not specified in the manuscript, then the approximated time point was considered according to the authors' judgment. Studies reporting study endpoints mentioned above, at least once, were included in the data synthesis. Dichotomous data were extracted either directly when the number of patients was mentioned, or indirectly by calculating back when reported as a percentage of patients. Further, these were converted into incidence (*n/N*) for pre-specified times. Individual definitions for the study outcomes (sensory, motor, analgesia, or side effects) were also accepted as described in each study. The incidence of any event was used for analysis if reported at least once in the patient. Events of side effects were extracted as dichotomous data and analyzed on an "intention to treat" basis. Dichotomous data were converted into incidence (*n/N*) for the time periods specified in the original manuscript. Studies with unreported or inconclusive data that could not be obtained after attempts to contact authors were excluded from this review.

Pairwise meta-analysis

A pairwise meta-analysis was conducted to assess the (1) efficacy and (2) safety of IT dexamethasone. The meta-analysis was conducted using Review Manager Software (RevMan 5.4.1, Cochrane Collaboration, Copenhagen, Denmark, 2014). A random-effects model was used for all analyses. Heterogeneity was measured and expressed as I^2. For continuous variables, mean differences (MDs) were compared using the inverse-variance (I–V) method. For dichotomous variables, the risk ratio (RR) was computed using the Mantel–Haenszel (M–H) method. Additionally, a secondary analysis was conducted comparing the study drug to other IT adjuvants such as dexmedetomidine or opioids.

Subgroup analysis and sensitivity analysis

Subgroup analysis was performed for a few of the outcomes of efficacy. Different doses (4 or 8 mg) of IT dexamethasone were evaluated. During sensitivity analysis, subjects of different population (such as pregnancy) were analyzed.

Risk of bias evaluation and trial sequential analysis

The risk of bias was assessed through the Cochrane risk of bias tool.[10] The risks of bias were then evaluated with a focus on random sequence generation, allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The disagreements between the review authors over the risk of bias were resolved by discussion. For all outcomes, the required information size (RIS) was checked using trial sequential analysis (TSA).

Grading of Recommendations Assessment, Development, and Evaluation

The certainty of the evidence was summarized using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for individual outcomes. The strength of recommendations reduced the potential to facilitate critical appraisal and improved the communication of judgments. GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, 2020 [developed by EvidencePrime, Inc.]) was used to facilitate the development of evidence summaries and recommendations.

Results

The database searches on March 26, 2023, yielded 6984 citations. We assessed 156 full texts for eligibility, and of these, 18 studies[11-28] provided the data for analysis. In none of the studies could additional information be obtained *via* e-mail from corresponding authors. Data from 2531 patients were included in the analysis. Figure 1 shows the list of studies along with reasons for their inclusion and exclusion.

Study characteristics [Table 1]

Based on our definitions, we identified 18 studies[11-28] that used IT dexamethasone in at least one study group for comparison. Thirteen studies[12-18,20,21,23,24,26,27] compared IT dexamethasone with saline, for sensory, analgesia, and motor effects. Three studies[11,15,19] compared it with IT dexmedetomidine, and four[18,22,25,28] with intravenous dexamethasone. With respect to beneficial/adverse effects 10 studies[12,15-18,20,23-25,28] provided data for analysis. The smallest[14] and the largest[11] studies in this review included 20 and 580 subjects, respectively. Four studies[16,19,24,27] included only cesarean deliveries, thirteen[11-15,17,18,20-23,26,28] had subjects undergoing general elective/emergency surgeries, and one[25] had unclear data. All studies used bupivacaine or levobupivacaine as the

Table 1: Table of study characteristics

Author, year	*n*	Age	Primary outcome	Secondary outcome	Surgery details	LA, dose	Study drug, dose	Control/ comparator, dose	Adverse events
Abdelhady 2022[11]	290/290	31±6/31±6	Duration of analgesic effects	Motor blockade, first analgesic request time	Obstetrics	Bupivacaine, 0.5%, 12.5 mg	Dexamethasone, 4mg	Dexmedetomidine, 10μg	Intraoperative shivering
Bani-Hasheem 2011[12]	25/25	37.8±12.33/35.08±11.33	Duration of sensory effects	Onset of sensory effects	Orthopedic surgery	Bupivacaine, 0.5%, 15mg	Dexamethasone, 8mg	Saline	hypotension, bradycardia, nausea, and vomiting, shivering
Bousabbeh 2022[13]	29/29	72.5±12.3/69.97±15.5	Duration of sensory block	Onset of sensory effects, pain free period, morphine consumption	Orthopedic femur surgeries	Bupivacaine, 0.5%, 10mg, sufentanil, 5μg	Dexamethasone, 8mg	Saline	Nausea and vomiting, itching
Dutta 2017[14]	10/10	33.11±10.21/35.26±12.11	Duration of sensory block	Onset, pain-free time	Abdominal surgery	Bupivacaine, 0.5%, 15mg	Dexamethasone, 8mg	Saline	
El-Hassan 2021[15]	20/20/20	33.80±8.70/34.80±8.9] 36.10±9.68	Duration of spinal anesthesia	Postoperative analgesia	Orthopedic surgery	Bupivacaine, 0.5%, 10mg	Dexamethasone, 4mg	Dexmedetomidine, 10μg or saline	Hypotension and bradycardia
El-Shourbagy 2019[16]	50/50	30.3±3.3/31.1±3.7	Duration of sensory block	Onset time	Obstetrics	Bupivacaine, 0.5%, 8-12mg	Dexamethasone, 8mg	Saline	Hypotension, bradycardia, nausea, and vomiting, shivering, headache/dyspnea
Elzayyat 2014[17]	20/20/20	35.9±9.7/36.2±11.8/35.4±10.2	Duration of spinal anesthesia	Postoperative analgesia	Lower abdominal surgeries	Bupivacaine, 0.5%, 12.5 mg	Dexamethasone, 4mg	Dexmedetomidine, 10μg or saline	Hypotension, bradycardia, nausea, and vomiting
Fawzy 2022[18]	210/210/210	35.1±8.8/35.6±8.7/35.6±8.1	Effect on PDPH	Onset and duration of sensory effects, pain-free period	Lower abdominal and lower limb surgeries	Bupivacaine, 0.5%, 15mg	Dexamethasone, 8mg	saline	hypotension, bradycardia, nausea, and vomiting, shivering
Ismaiel 2020[19]	30/30	28.7±2.7/29.2±2	Prevention of perioperative shivering	Postoperative Analgesia	Obstetrics	Bupivacaine, 0.5%, 12.5 mg	Dexamethasone, 8mg	Dexmedetomidine, 5μg	Hypotension, bradycardia, nausea, and vomiting
Kaur 2021[20]	35/35/35	NP	Duration of spinal anesthesia	onset, postoperative analgesia	Orthopedic surgery	Bupivacaine, 0.5%, 12.5mg	Dexamethasone, 4mg	Saline or, fentanyl, 25μg	Hypotension, bradycardia, nausea, and vomiting, shivering, pruritis
Khaleel 2021[21]	50/50	65.4±13.4/68.7±13.2	Duration of spinal anesthesia	Hemodynamic and complications	Orthopedic surgery, total hip replacement	Bupivacaine, 0.5%, 15mg	Dexamethasone, 8mg	Saline	Shivering

Contd...

Table 1: Contd...

Author, year	*n*	Age	Primary outcome	Secondary outcome	Surgery details	LA, dose	Study drug, dose	Control/ comparator, dose	Adverse events
Kiasari 2022[22]	60/60	29.1±5.5/30.1±5.1	Effect on complications of IT morphine during spinal anesthesia	Onset and level of sensory effects, analgesia effects	Obstetrics	Bupivacaine, 0.5%, 10mg	Dexamethasone, 8mg	IV Dexamethasone, 8mg, sterile water	Nausea, vomiting, itching
Moeen 2017[23]	30/30/30	67.8±3.45/68.5±3.36/68.9±2.92	Prevention of shivering	Duration of spinal anesthesia, duration of postoperative analgesia	TURP	Bupivacaine, 0.5%	Dexamethasone, 8mg	Meperidine 0.2mg/ kg, or saline	Sedation, hypotension, bradycardia, nausea, and vomiting, shivering, pruritis
Mohammed 2018[24]	30/30/30	26.93±5.47/26.83±5.50/25.70±5.55	Duration of spinal anesthesia	Frequency of adverse effects	Obstetrics	Bupivacaine, 0.5%, 12.5mg	Dexamethasone, 2mg and 4mg	saline	hypotension, bradycardia, nausea, vomiting, shivering, PDPH
Pyasetska 2020[25]	52/51/51	NP	Prevention of arterial hypotension	None	NP	Bupivacaine, 0.5% 10mg	Dexamethasone, 4mg and 8 mg	Saline	Nausea, vomiting, bradycardia, and shivering
Sakic 2019[26]	30/30	NP	Occurrence of postoperative disturbance of consciousness and plasma cortisol level	Pain intensity, blood glucose levels, and recovery	Orthopedic surgery	Levobupivacaine, 12.5mg	Dexamethasone, 8mg		
Tabatabaei 2022[27]	35/35	27.1±6.2	Mean time to start of anesthesia	Duration of postoperative analgesia	Obstetrics	Bupivacaine, 0.5%, 12.5mg	Dexamethasone, 4mg		Nausea/vomiting
Tkachenko 2021[28]	41/42/41	NP	Management of nausea and vomiting	Hypotension, shivering	Obstetrics	Bupivacaine, 0.5%, 11mg, fentanyl, 10μg, and morphine, 100μg	Dexamethasone, 4mg	Saline or intravenous ondansetron	Arterial hypotension, nausea, vomiting, shivering

IT, intrathecal; IV, intravenous; LA, local anesthetic; N, number of subjects; NP, not provided; PDPH, post-dural puncture headache; TURP, transurethral resection of prostate

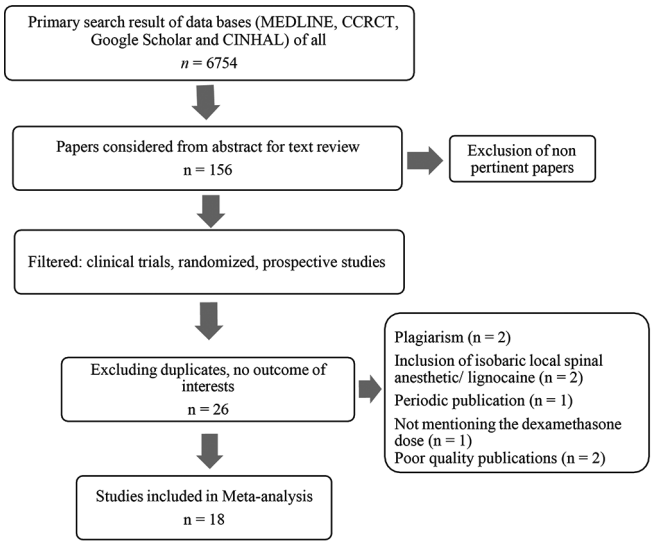

Figure 1: The flowchart for literature identification and study selection

primary IT local anesthetic agent for SAB. The minimum/maximum doses of IT local anesthetic (bupivacaine) dose and IT dexamethasone were 8/15 mg and 2/8 mg, respectively. Adverse effects included hypotension (10 studies[12,15-18,20,23-25,28]), bradycardia (9 studies[12,15-18,20,23-25]), nausea, and vomiting (11 studies[12,13,16-18,20,23-25,27,28]), shivering (9 studies[12,16,18,20-25,28]), pruritis (3 studies[13,20,23]), and PDPH (2 studies[18,24]). The reported dichotomous data of nausea and vomiting were handled differently from other observed events. The "overall" nausea and vomiting events over the duration of the study were considered because they were not reported separately in some of the studies. If incidences of nausea and vomiting were reported separately, then the higher value was taken into consideration. Because occurrence of one does not exclude the other, nausea, and vomiting events were not added up.

Sensory effects

The results of the pairwise meta-analysis showed the superiority of using adjuvant IT dexamethasone over IT bupivacaine alone [Figure 2a-d] with respect to sensory blockade. Addition of dexamethasone to bupivacaine prolonged the sensory blockade duration (MD = 63.8 minutes; [95% CI, 33.1, 94.5], overall effect $P < 0.0005$, $I^2 = 100\%$ and P [I^2] <0.0001), 2-segment regression time (MD = 20.1 minutes; [95% CI, 0.96, 39.2], overall effect $P = 0.04$, $I^2 = 80\%$ and P [I^2] =0.03), and first rescue analgesic time (MD = 143.1 minutes; [95% CI, 90.3, 196.0], overall effect $P < 0.0001$, $I^2 = 100\%$ and P [I^2] <0.0001).

Subgroup analysis (dexamethasone, 4 vs 8 mg) showed that the duration of sensory blockade was prolonged with either dose. Five studies for each subgroup were included; however, the TSA RIS was met only for the dose of 8 mg (TSA RIS, n = 1963 and 164, for 4 and 8 mg groups, respectively). Further, the first rescue analgesic request time had statistically significant results for 8 mg doses (MD = 153.7 minutes; [95% CI, 59.7, 247.6], overall effect $P = 0.001$, $I^2 = 100\%$ and P [I^2] <0.0001) and met the RIS (TSA RIS, n = 77).

The onset time of sensory blockade was not reduced by dexamethasone. The overall effects observed were statistically not significant for bupivacaine (MD = -0.55 minutes; [95% CI, -1.14, -0.04], overall effect $P = 0.07$, $I^2 = 88\%$ and P [I^2] <0.0001).

Motor effects

Seven studies[15-17,20,21,23,27] reported motor effects related to dexamethasone use [Figure 3]. There were no statistically significant differences recorded for onset (MD = -0.46 minutes; [95% CI, -1.98 to 1.05], overall effect $P = 0.55$, $I^2 = 56\%$ and P [I^2] =0.55), and for duration of motor blockade, at 8 mg doses (MD = 33.6 minutes; [95% CI, -3.7 to 70.8], overall effect $P = 0.08$, $I^2 = 100\%$ and P [I^2] <0.0001).

Beneficial or adverse effects

Significantly lower RRs were recorded for SAB-associated side effects in the dexamethasone group *viz.* for hypotension (RR = 0.74; [95% CI, 0.6, 0.9], $P = 0.0003$, $I^2 = 0\%$, TSA RIS, n = 988) and for nausea and vomiting [RR = 0.62; 95% CI, 0.41, 0.93], $P = 0.02$, $I^2 = 39\%$, TSA RIS, n = 1632, Figure 4]. Though lower RRs were observed for bradycardia, shivering, pruritis, PDPH, etc., they did not reach statistical significance. No study reported short or long-term adverse effects specific to dexamethasone use.

Comparisons to intravenous dexamethasone, IT dexmedetomidine, or IT opiates

The sensory efficacy and beneficial/adverse effects recorded for analysis did not favor intravenous dexamethasone [Supplementary Data 2], IT dexmedetomidine [Supplementary Data 3], or IT opiates, except for the outcome of hypotension episodes during SAB. In a small group of subjects (three studies,[18,25,28] n = 606), adjuvant IT dexamethasone had lower RRs for hypotension episodes compared to intravenous use of similar doses [RR = 0.62; 95% CI, 0.43, 0.89], $P = 0.009$, $I^2 = 0\%$, TSA RIS, n = 989, Supplementary Data 2].

Risk of bias and GRADE

The risk of bias is depicted in Figure 5. Among 126 items, low, high, and unclear risk of bias were accorded in 65, 7, and 54 items, respectively. Two studies[15,18] had a low risk of bias for selection, performance, detection, attrition, or reporting. The relevant GRADE summary results are presented in Supplementary Data 4. The majority of the included studies reported homogenous outcomes on our primary outcomes, and therefore, indirectness

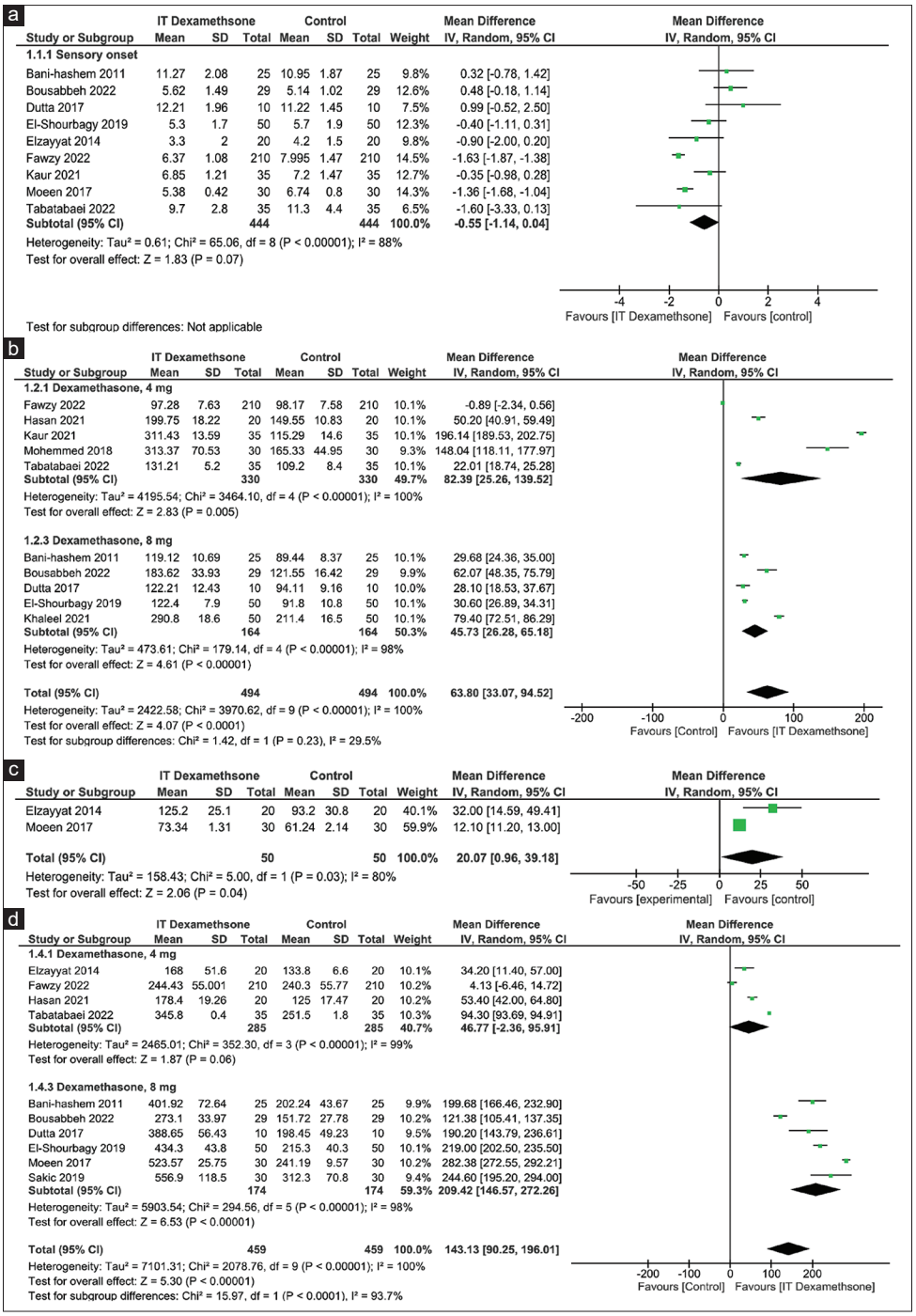

Figure 2: The forest plot depicting IT dexamethasone versus control comparisons for sensory and analgesia effects, (a) Onset of sensory blockade, (b) Duration of sensory blockade, (c) 2-segment regression time, and (d) Analgesia duration or first rescue analgesic request. The mean differences between individual trials and 95% CIs are shown. Absolute values are expressed in minutes. The overall effects and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. CI: confidence interval, IT: intrathecal, IV: inverse-variance, SD: standard deviation

was minimal. However, in terms of inconsistency of results (and range of CIs), we downgraded the summary evidence. The certainty of the evidence is summarized as 'moderate' for the outcome of the duration of sensory blockade and "first rescue analgesia request time" with 8 mg dose. The certainty of the evidence for motor effects was described as "low."

Discussion

Our meta-analysis attempts to investigate the effects and safety of adjuvant IT dexamethasone along with conventional local anesthetics during SAB. Our results confirm that IT dexamethasone at 4 or 8 mg dosage prolongs sensory

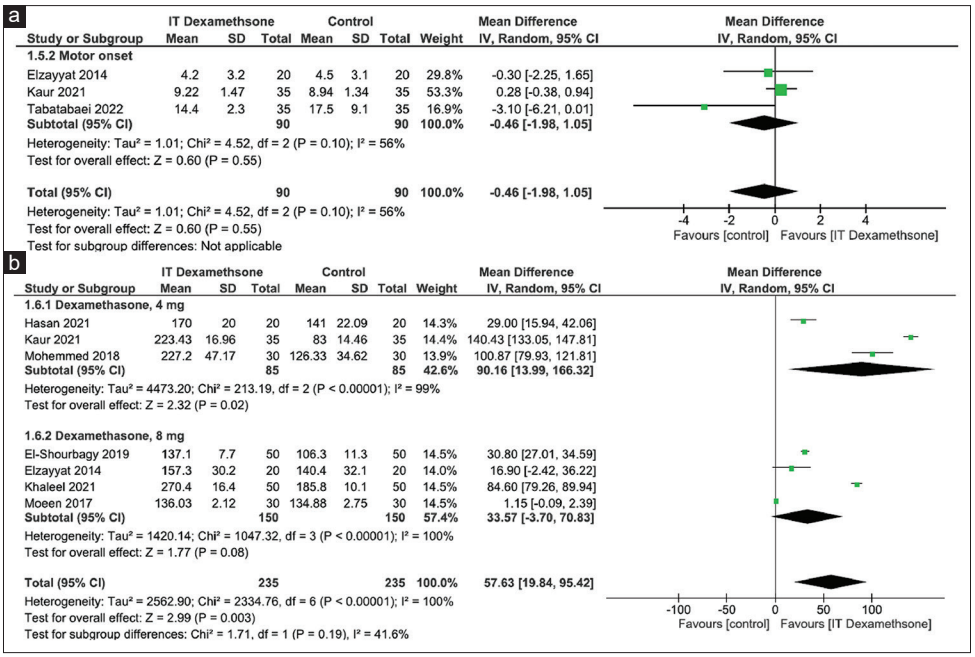

Figure 3: The forest plot depicting IT dexamethasone versus control comparisons for motor blockade, (a) onset of motor blockade, (b) duration of motor blockade. The mean differences between individual trials and 95% CIs are shown. Absolute values are expressed in minutes. The overall effects and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. CI: confidence interval, IT: intrathecal, IV: inverse-variance, SD: standard deviation

block as well as increases the 'time to demand' for the first rescue analgesia. We have no definitive evidence that dexamethasone prolongs motor blockade. Additionally, lower RRs were observed for SAB-linked adverse effects such as hypotension, nausea, and vomiting. In a secondary analysis comparing the effects of adjuvant IT dexamethasone to intravenous administration, we observed no additional benefit.

Prolongation of sensory and motor effects of local anesthetics in regional peripheral nerve blocks with adjuvant dexamethasone is well recognized.[29,30] Epidurally administered dexamethasone has been proven to prolong analgesia and other sensory effects. A few studies have demonstrated a reduction of local anesthetic dosage requirement in SAB with the use of adjuvant IT dexamethasone.[31,32] However, its dose and safety profile have not been well studied. This is the most comprehensive meta-analysis of outcomes associated with neuraxial dexamethasone to date. We included an adequate number of studies to analyze the main outcomes. Subgroup analyses revealed superior effects of 8 mg dose over 4 mg for sensory and analgesic effects. We observed that dexamethasone via the IT route additionally prolongs the sensory effects of local anesthetics by an approximate mean time of one hour and delays the first rescue analgesic time by 2-3 hours. Our sensitivity analysis of the cesarean population including data from four studies[16,19,24,27] revealed similar beneficial results with regard to the duration of sensory blockade and first analgesic request time [Supplementary Data 5].

Lower RRs of SAB-related hypotension episodes, nausea, and vomiting were recorded for the dexamethasone group. This confers additional advantages in a situation of prolonged sensory blockade. During TSA for hypotension episodes, the *z*-curve surpassed the trial sequential monitoring boundaries for statistical significance and met the RIS of participants. Sensitivity analysis paradoxically revealed that 4 mg dose (seven studies, $P = 0.005$, $I^2 = 0\%$) effectively reduced hypotension episodes while 8 mg dose did not (three studies, $P = 0.35$, $I^2 = 46\%$). An explanation for this could be that the number of studies using 8 mg dose available for the above analysis was smaller. While the suppressive effect of intravenous dexamethasone on nausea and vomiting[33] is already proven, we extended our analysis to compare it to the IT method. Hypotension, nausea, and vomiting episodes were lesser with IT than intravenous dexamethasone. Though a few authors claim that many of the SAB-associated side effects are prevented by IT dexamethasone,[33-36] we could not confirm these benefits for side effects such as shivering and PDPH.

Animal studies have provided a few insights into the systemic and local effects of IT dexamethasone. Intrathecal administration of dexamethasone as a premedication has been reported to be safe and devoid of any damaging histological changes to neural tissue.[37] Yet another animal

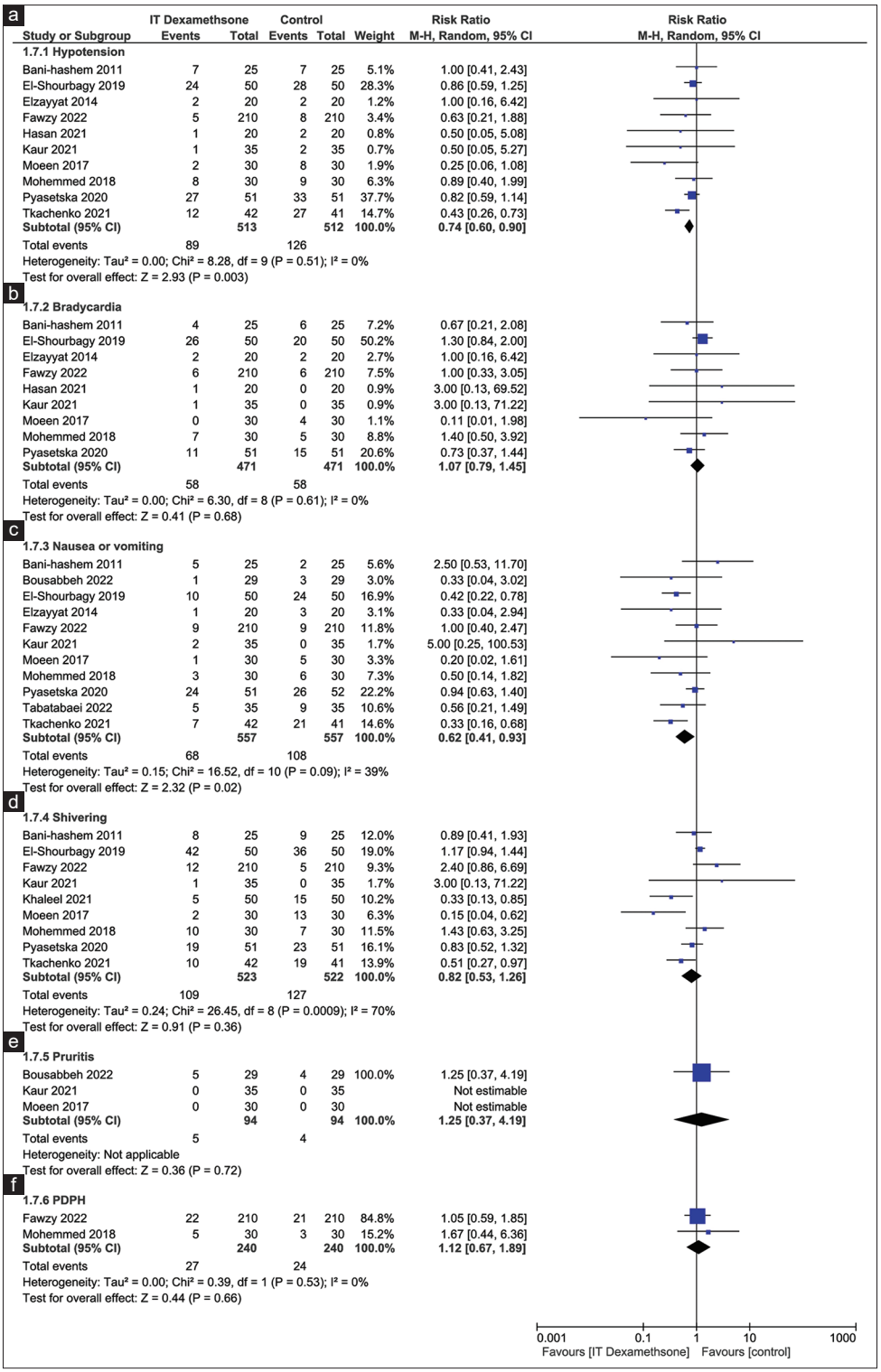

Figure 4: The forest plot depicting IT dexamethasone versus control comparisons for adverse effects, (a) hypotension, (b) bradycardia, (c) nausea and vomiting, (d) shivering, (e) pruritis, and (f) PDPH. The mean differences between individual trials and 95%CIs are shown. Absolute values are expressed for incidences. The overall effects are expressed as risk ratios. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. CI: confidence interval, IT: intrathecal, MH: Mantel–Haenszel, PDPH: post-dural puncture headache, SD: standard deviation

study using chronic continuous IT infusion of dexamethasone revealed that high dose (125 ng/h) caused significant intrathecal inflammation while low dose (12.5 ng/h) did not.[38] Our meta-analysis comprising a relatively large number of subjects receiving IT dexamethasone (n = 1078) reveals no severe, long, or short-term adverse outcomes during the study period. Included studies, however, focused more on evaluations related to beneficial effects rather than

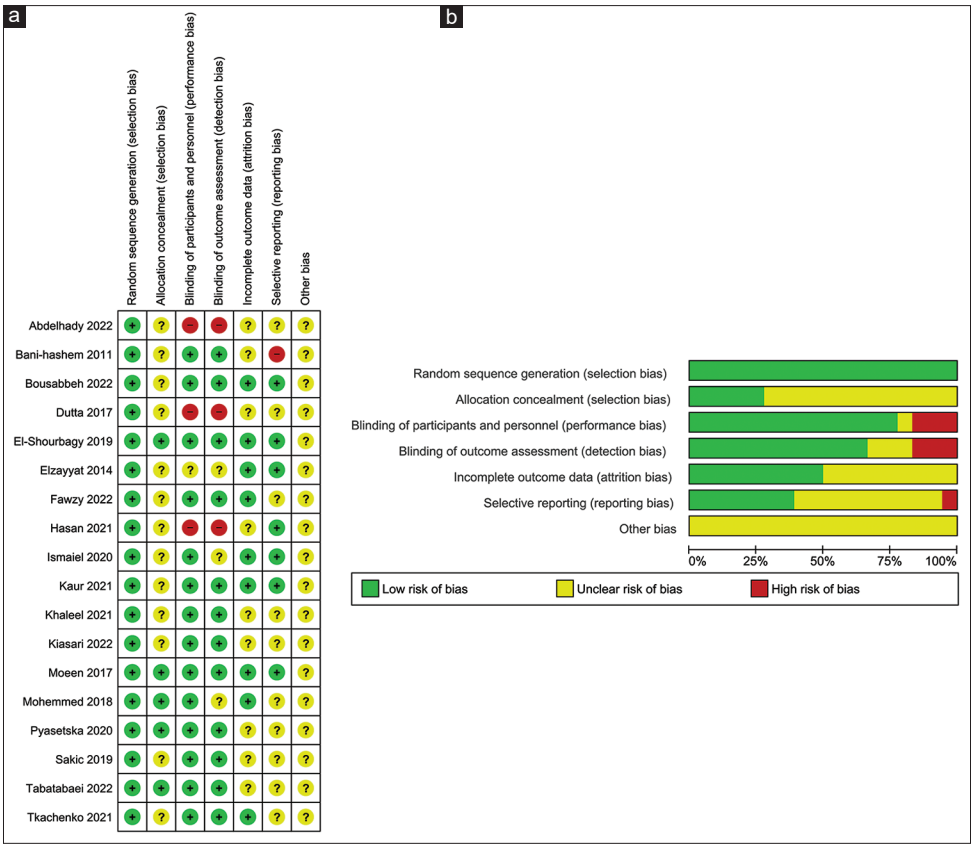

Figure 5: Risk of bias summary and graph. (a) Risk of bias and (b) Graph

adverse outcomes. There are also safety concerns expressed over the systemic administration of dexamethasone. Dexamethasone (intravenous 2 mg at repeated doses) suppresses cortisol levels to less than 5% of baseline at 24 hours, and these return to normal on the subsequent day.[39] Isolated human case reports mention suppression of the adreno-cortical axis, leading to secondary adrenal insufficiency.[39] While a single dose of dexamethasone is unlikely to cause such an adverse event, the remote possibility of its occurrence cannot be dismissed.[40] Similarly, IT dexamethasone has induced lower plasma cortisol levels in a small group of patients treated for chronic pain.[39] Neuroendocrine responses are, however, different in surgical patients. One of the studies in our meta-analysis claims reductions in cortisol levels in patients with hip fractures who received IT dexamethasone with the SAB.[26] It yet remains unclear if IT dexamethasone administration can induce less adrenal suppression than the intravenous method. Interestingly, IT dexamethasone has been used safely in treating post-traumatic visual disturbances, as reported in a study involving over 2000 injections in more than 200 subjects.[41] Neuraxial steroid preparations are extensively being used in regular clinical practice, though the American Food and Drug Administration organization has not as yet approved their use.[42]

The analgesic benefit of perineural over the systemic route is amply demonstrated in a recent study of ulnar nerve blocks in healthy volunteers.[43] The jury is out on perineural versus systemic administration of dexamethasone with respect to analgesic effect as well as safety profile. Convincing clinicians to use the IT route over intravenous would be challenging. Establishing an acceptable safety profile would be a critical issue in this regard. Our meta-analysis clearly shows the analgesic benefits of adjuvant IT dexamethasone. With regard to safety, existing studies suggest that IT route is at least on par with the intravenous route. Neuraxially administered dexamethasone reduces the nociceptive signal transmission in the dorsal roots of the spinal cord. It is possible that locally acting adjuvants can induce much lesser systemic side effects when compared to intravenous methods. Additionally, one should take into account that concomitant IT administration of dexamethasone alongside the local anesthetic does not involve a second invasive maneuver. There is thus sufficient case for recommending the IT route over systemic administration.

The current meta-analysis has a few limitations; for example, the limited sample size, especially in a subgroup of cesarean subjects. Higher heterogeneity among the study groups was recorded for a few of the studied parameters. Our explanation for existing high heterogeneity is the use of different doses

of heavy bupivacaine. Also, in few study groups, additional opioids were administered through the subarachnoid route, which caused the differences in duration of sensory effects, thus contributing to heterogeneity. A few additional variables were considered *viz*. IT administration of saline or sterile water along with the local anesthetics and the type of surgery in the included population. To minimize these variables, we included only hyperbaric bupivacaine or hyperbaric levobupivacaine as spinal anesthetics in our study. Isobaric solutions or agents such as ropivacaine[31] or lignocaine[44] were not considered. Considering the study methodology, variation was identified between the study design, bias, and definitions of a few outcomes. There were insufficient number of procedures in specific surgical categories to enable differentiation between procedure types. Significant bias was identified in terms of performance and selective reporting for few studies. Sharma *et al*.[45] and Sonker *et al*.[46] reported data without SDs. Interestingly, both studies recorded unnatural reduction in duration of sensory block when IT dexamethasone was used as an adjuvant. We excluded these two studies with uncertain data and a high risk of bias. Some of the outcomes were underpowered or did not meet the RIS during TSA and hence no conclusions could be drawn; for example, duration of sensory blockade (4 mg dose), motor blockade, incidence of bradycardia and shivering. Further, the adverse effect analysis specific to IT use was not possible owing to the paucity of data.

Conclusions

IT dexamethasone, used as an adjuvant to spinal local anesthetics, increases sensory blockade duration and the time for request of the first rescue analgesic. A dose of 8 mg appears to be superior to 4 mg in this setting. The optimal intrathecal dose has yet to be decided, and meaningful conclusions can be made only if high-quality RCTs are available. SAB induced side effects such as hypotension, nausea, and vomiting are lesser with the use of IT dexamethasone.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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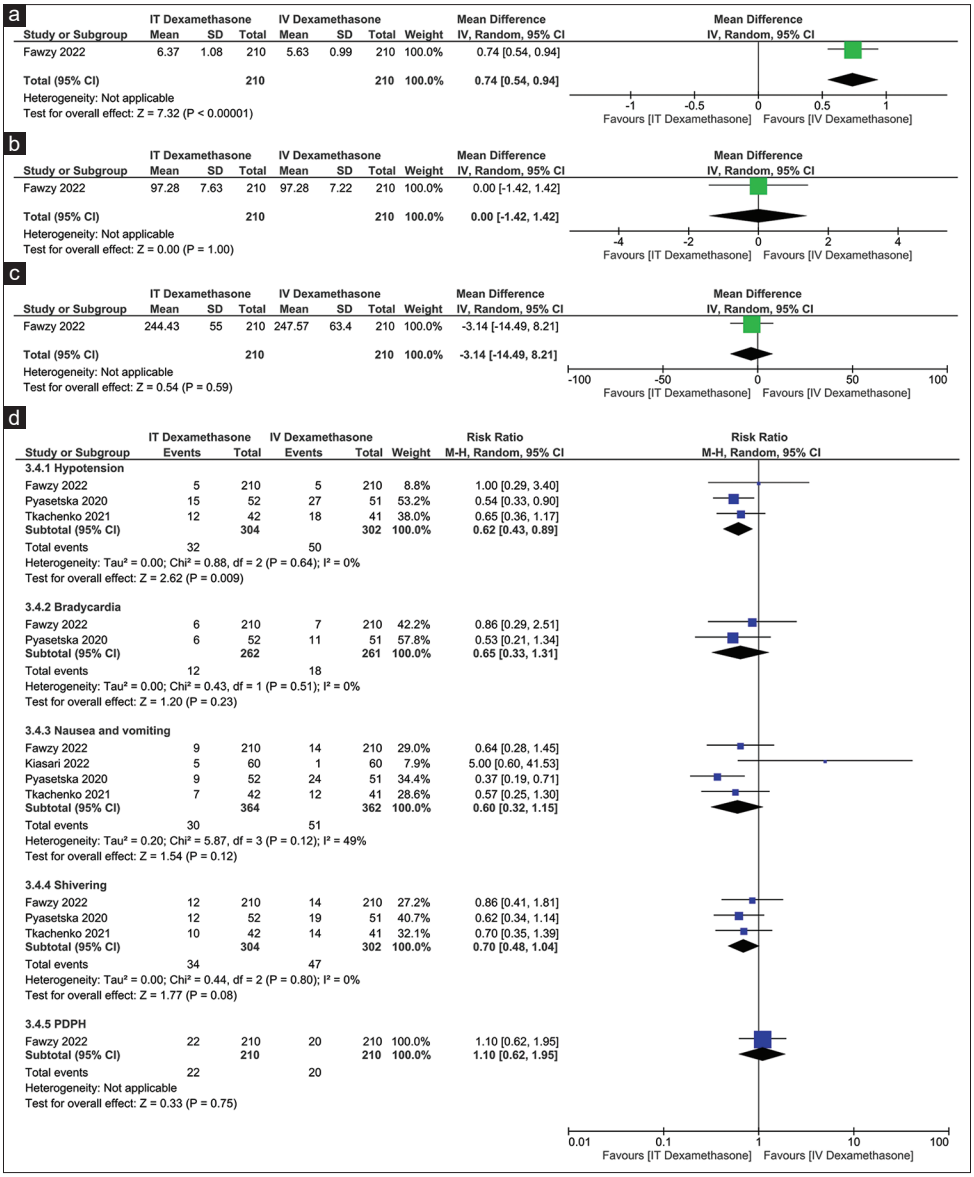
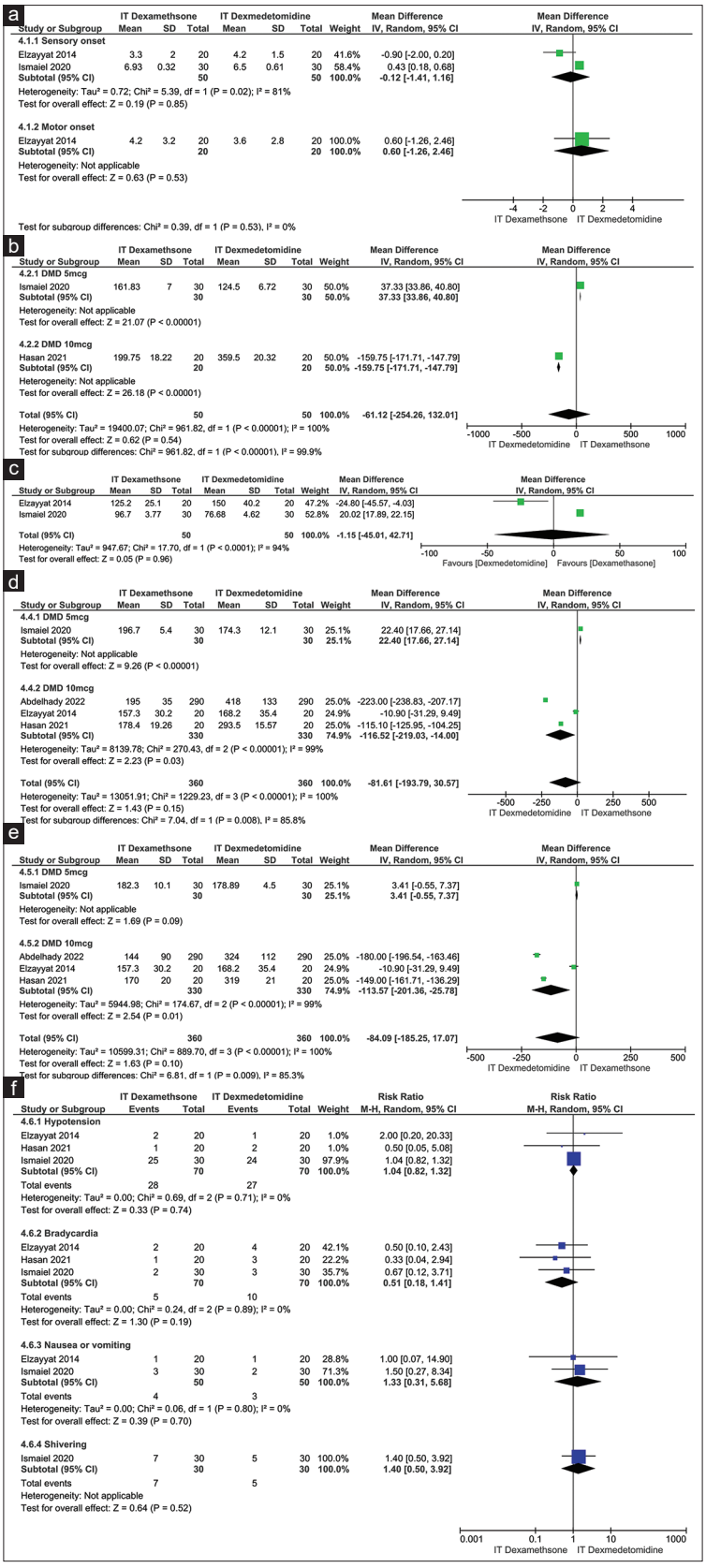
20	1 or 2 or 3 or 13 or 14 or 15 or 16 or 17 or 18 or 19	782,680
21	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	5,445,600
22	4 and 20 and 21	19,019

Supplementary Data 1: The search strategy



Supplementary Data 2: Forest plots comparisons of IT dexamethasone to intravenous dexamethasone during spinal anesthesia. (a) Onset of sensory and motor effects, (b) duration of sensory blockade, (c) two-segment regressions, (d) first rescue analgesic request, (e) duration of motor blockade, (f) beneficial or adverse effects. CI, confidence intervals; DMD, dexmedetomidine; IT, intrathecal; IV, inverse-variance; IV, intravenous; SD, standard deviation



Supplementary Data 3: Forest plots comparisons of IT dexamethasone to dexmedetomidine during spinal anesthesia. (a) Onset of sensory and motor effects, (b) duration of sensory blockade, (c) 2-segment regressions, (d) first rescue analgesic request time, (e) duration of motor blockade, and (f) beneficial or adverse effects. CI, confidence intervals; DMD, dexmedetomidine; IT, intrathecal; IV, inverse-variance; SD, standard deviation

Author(s): Dr Thrivikrama Padur Tantry, M.D., and others

Question: Intrathecal dexamethasone for spinal anesthesia

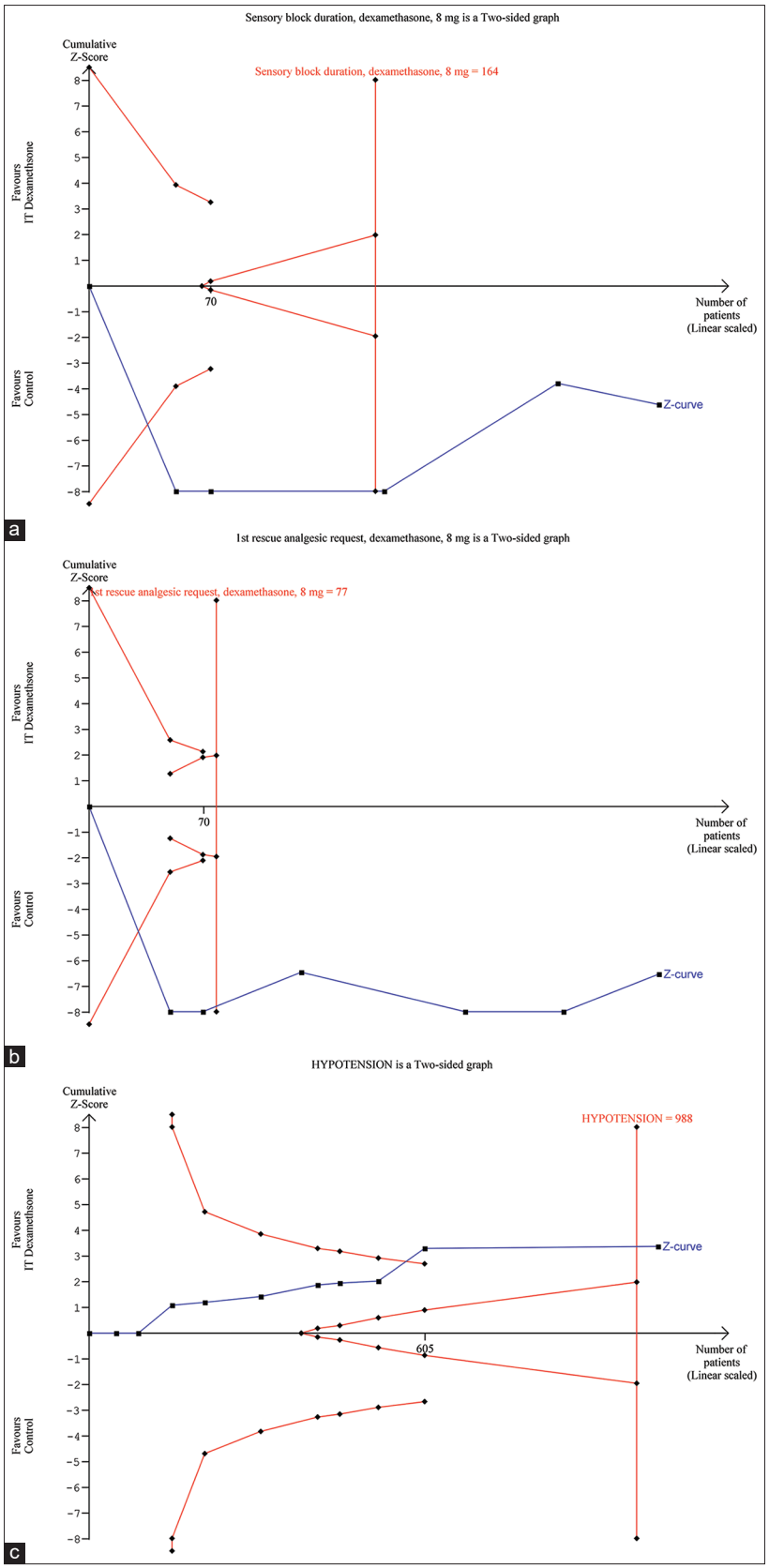
Setting: Subarachnoid blockade

Bibliography: Efficacy and safety of intrathecal dexamethasone during spinal anesthesia; a systematic review and meta-analysis

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spinal anesthesia effects,	saline	Relative (95% CI)	Absolute (95% CI)	
Sensory onset - Sensory onset, bupivacaine											
9	randomised trials	not serious	serious	not serious	not serious	none	444	444	-	MD **0.55 lower** (1.14 lower to 0.04 higher)	⊕⊕⊕◯ Moderate
Sensory block duration											
10	randomised trials	not serious	serious	serious	not serious	none	494	494	-	MD **63.8 higher** (33.1 higher to 94.5 higher)	⊕⊕⊕◯ Moderate
Sensory block duration – dexamethasone, 4 mg											
5	randomised trials	not serious	serious	not serious	serious	none	330	330	-	MD **82.4 higher** (25.3 higher to 139.5 higher)	⊕⊕◯◯ Low
Sensory block duration – dexamethasone, 8 mg											
5	randomised trials	not serious	not serious	not serious	serious	none	164	164	-	MD **45.7 higher** (26.3 higher to 65.2 higher)	⊕⊕⊕◯ Moderate
2-segment regression											
2	randomised trials	not serious	serious	not serious	not serious	RIS	50	50	-	MD **20.07 higher** (0.96 higher to 39.18 higher)	⊕⊕◯◯ Low
1st-rescue analgesic request											
10	randomised trials	not serious	serious	not serious	not serious	none	459	459	-	MD **143.1 higher** (90.3 higher to 196.1 higher)	⊕⊕⊕◯ Moderate
1st-rescue analgesic request – dexamethasone, 4 mg											
4	randomised trials	not serious	serious	not serious	not serious	none	285	285	-	MD **46.8 higher** (-2.36 lower to 95.9 higher)	⊕⊕⊕◯ Moderate
1st-rescue analgesic request – dexamethasone, 8 mg											
6	randomised trials	not serious	serious	not serious	not serious	none	174	174	-	MD **209.4 higher** (146.9 higher to 272.3 higher)	⊕⊕⊕◯ Moderate
Motor onset											
3	randomised trials	not serious	serious	not serious	not serious	none	90	90	-	MD **0.46 lower** (1.98 lower to 1.05 higher)	⊕⊕⊕◯ Moderate
Motor blockade duration											
7	randomised trials	not serious	serious	not serious	not serious	RIS	185	185	-	MD **53.05 higher** (14.25 higher to 91.86 higher)	⊕⊕◯◯ Low
Motor blockade duration - dexamethasone, 4 mg											
3	randomised trials	not serious	serious	not serious	not serious	RIS	80	80	-	MD **65.05 higher** (3.6 lower to 133.7 higher)	⊕⊕◯◯ Low
Motor blockade duration - dexamethasone, 8 mg											
4	randomised trials	not serious	serious	not serious	not serious	RIS	105	105	-	MD **46.96 higher** (33.45 lower to 127.36 higher)	⊕⊕◯◯ Low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Supplementary Data 4: The GRADE evidence for sensory and motor outcomes



Supplementary Data 5: Trial sequential analysis (TSA) of (a) sensory block duration for 8 mg of IT dexamethasone, (b) first rescue analgesic request time for 8 mg of IT dexamethasone, and (c) hypotension episodes risk ratios, demonstrating required information size (RIS). The Z-value is the test statistic and |Z| =1.96 corresponds to a *P* = 0.05. The RIS for these outcomes was checked using a random effects (DL, Lan-DeMets') model using existing MDs or RRs and diversity (D^2) of each subgroup, with a double-sided alpha of 0.05 and beta of 0.20 (power of 80%)