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Effectiveness of Nebulized Dexmedetomidine in Managing Post-Dural Puncture Headache in Obstetric patients: A Systematic Review

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Abstract: Post-dural puncture headache (PDPH) is a common complication after neuraxial anesthesia in obstetrics. While the epidural blood patch (EBP) remains as the gold-standard treatment, less invasive strategies are being increasingly explored. One such intervention is dexmedetomidine (DEX), an alpha-2-adrenergic agonist with analgesic and sedative properties. Method: A comprehensive literature search of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted. Studies evaluating nebulized dexmedetomidine for the treatment of PDPH following neuraxial anesthesia in obstetric patients were included. Comparator groups included saline (placebo), fentanyl, and neostigmine/atropine. The primary outcome was reduction in headache severity measured using the Visual Analog Scale (VAS). Secondary outcomes included adverse events and the need for additional interventions, including epidural blood patch. Two reviewers independently screened studies, extracted data, and assessed risk of bias. Results: Five studies met the inclusion criteria. In most studies, nebulized dexmedetomidine was administered at a dose of 1 µg/kg diluted to a total volume of 4 mL and given every 12 hours for up to 72 hours. Compared with placebo, dexmedetomidine consistently reduced VAS pain scores at 24, 48, and 72 hours and decreased the need for additional treatments. Compared with fentanyl, dexmedetomidine provided superior headache relief, while demonstrating comparable efficacy to neostigmine/atropine. Patients receiving dexmedetomidine were less likely to require rescue therapies or epidural blood patch. Reported adverse events were infrequent and generally mild, including sedation, dry mouth, and bradycardia. Conclusion: Nebulized dexmedetomidine appears to be a safe, effective, and minimally invasive treatment option for PDPH in obstetric patients. It is associated with meaningful reductions in headache severity and may decrease the need for invasive interventions such as epidural blood patch. Larger, high-quality multicenter randomized controlled trials are needed to confirm these findings and define the role of nebulized dexmedetomidine in routine clinical practice.

Keywords: Dexmedetomidine, neuraxial anesthesia, obstetric anesthesia, post-dural puncture headache, postpartum

INTRODUCTION

Post-dural puncture headache (PDPH) is among the most common and debilitating complications following spinal anesthesia and accidental dural puncture during epidural

placement. The headache characteristically worsens in the upright position and improves when lying supine (1). Associated symptoms often include neck stiffness, nausea, photophobia, tinnitus, and cranial nerve dysfunction (1,2). The reported incidence of PDPH ranges widely from 0.5% to 28% (3,4). Pregnant women are especially at risk, and the condition can significantly increase maternal morbidity, healthcare costs, hospital stay duration, and patient dissatisfaction, while also impairing maternal–infant interaction (1,3,4).

It is well established that PDPH is primarily linked to cerebrospinal fluid (CSF) leakage from the intrathecal space, although the exact pain mechanisms remain unclear (1). One hypothesis suggests that after delivery, reduced epidural pressure increases CSF leakage through a dural defect, causing downward traction on the pain-sensitive meninges (3). Additionally, the Monro-Kellie hypothesis and low substance P levels in CSF are also potential risk factors (5,6)

Despite advances in needle design, accidental dural punctures during epidurals and PDPH remain common challenges in obstetric anesthesia, causing maternal discomfort, delayed recovery, and impaired maternal-infant bonding. Effective and safe management strategies are therefore crucial to improving postpartum outcomes and overall patient satisfaction.

The epidural blood patch (EBP) remains the gold standard for managing PDPH due to its well-established efficacy and favorable benefit–to–risk profile (1). However, EBP is invasive and carries potential complications such as back pain, radicular symptoms, transient bradycardia, fever, seizures, and meningeal irritation (7). A non-invasive pharmacologic alternative would therefore be advantageous.

Dexmedetomidine is a selective α_2-adrenergic receptor agonist with analgesic, anxiolytic, and sympatholytic properties, and it produces minimal respiratory depression (8). Although initially, approved for short-term sedation, its off-label applications have expanded considerably in recent years.

The purpose of this review is to evaluate the efficacy of nebulized dexmedetomidine as a treatment modality for obstetric PDPH. The primary outcome is a reduction in patient-reported pain intensity measured by the Visual Analog Scale (VAS). Secondary outcomes include the need for additional interventions (including EBP) and the incidence of adverse effects.

METHODS

This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive literature search was performed in MEDLINE, EMBASE, Web of Science, and Google Scholar till April 2025 to identify studies evaluating the use of nebulized dexmedetomidine for the management of post-dural puncture headache (PDPH) in obstetric patients. The search strategy used a combination of MeSH terms, EMTree descriptors, and keywords related to Nebulized Dexmedetomidine, Post-Dural Puncture Headache, and Neuraxial anesthesia in Obstetric patients. To ensure comprehensive identification of eligible studies, the reference lists of all included articles were manually searched. Google Scholar search was also performed to identify potentially relevant studies not indexed within the selected databases.

Eligibility Criteria

Studies were included if they evaluated the use of nebulized dexmedetomidine for the treatment or management of PDPH in obstetric patients. We included observational studies, cohort studies, case reports, randomized control trials, clinical trials, and multicenter studies. No restrictions were placed on the publication year or geographical settings, and conference publications.

Study Selection

All the compiled literature from the databases was imported into Covidence systematic review software to manage citations. Automatic checks for duplicate entries were performed by using Covidence. Selected articles were screened by title and abstract, followed by a full-text assessment to ensure that these articles did indeed meet the eligibility criteria. Article selection was carried out by two independent reviewers with disagreements being resolved through a consensus decision. The PRISMA flowchart (Figure 1) displays the study selection process.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data collection form. Extracted data included study design, patient characteristics, obstetric and anesthetic variables, dexmedetomidine dosing and administration details, comparator interventions, clinical outcomes related to PDPH, adverse events, and key study findings.

Risk of Bias Assessment

Methodological quality was assessed independently by two reviewers. Randomized controlled trials were evaluated using the Cochrane Risk of Bias tool, and Case reports and case series were appraised using the Critical Appraisal Checklists.

Data Synthesis

Due to the expected variability in study designs, patient groups, treatments, and outcome measures, we have summarized the findings clearly. The results were organized by study type, treatment details, clinical outcomes, and reported side effects.

RESULTS

Our literature search identified five eligible studies comprising a total of 290 patients. Among these, 115 patients received nebulized dexmedetomidine for the management of post-dural puncture headache (PDPH) after spinal anesthesia for cesarean section. Four studies were randomized controlled trials (RCTs), while one was a two-patient case report without a comparator group. The RCTs compared nebulized dexmedetomidine against fentanyl, saline, a combination of saline and fentanyl, or neostigmine/atropine. The case report described the effects of nebulized dexmedetomidine on PDPH symptoms after labor

epidural. Baseline patient characteristics were generally comparable across studies (Table 1). The mean age ranged from 25 to 29 years, and most participants were classified as American Society of Anesthesiologists (ASA) physical status II. Body weight and body mass index (BMI) were inconsistently reported, with mean body weight ranging from approximately 52 to 55 kg.

Intervention Characteristics

Nebulized dexmedetomidine was the primary intervention evaluated across all included studies (Table 2). However, treatment protocols varied considerably. Two randomized controlled trials administered nebulized dexmedetomidine at a dose of 1 µg/kg twice daily for up to three days.[9,12] One study continued treatment until patients achieved both a Visual Analog Scale (VAS) pain score of ≤3 and a Lybecker classification score of <2.[11] Another trial evaluated a single administration of nebulized dexmedetomidine at a dose of 1 µg/kg.[2] In one study, the dosing regimen was not reported. [10]

Primary Outcome

Pain severity, was the primary outcome across all included studies (Table 3) and it was measured using the Visual Analog Scale (VAS; range 0–10), VAS scores were assessed at baseline (T0) and at 24 hours (T1), 48 hours (T2), and 72 hours (T3) following initiation of treatment. All studies demonstrated a reduction in pain scores over time among patients receiving nebulized dexmedetomidine. Kumar et al.[9] reported a decrease in mean VAS scores from 7 ± 2 at baseline to 1 ± 1 at 72 hours. Similarly, Garg et al.[10] observed a reduction from 6.8 ± 1.2 at baseline to 1.2 ± 0.8 at 72 hours. Across the randomized controlled trials, improvements in pain scores were consistently greater in the nebulized dexmedetomidine groups than in the comparator groups, suggesting superior analgesic efficacy. Overall, the available evidence indicates that nebulized dexmedetomidine is associated with sustained reductions in pain severity during the first 72 hours of treatment.

Secondary Outcomes

Secondary outcomes included adverse events and the need for rescue therapies, such as oral paracetamol, oral caffeine, and epidural blood patch (EBP) (Table 4). Overall, the requirement for additional interventions was lower among patients receiving nebulized dexmedetomidine. In the study by Kumar et al.[9] only six patients in the dexmedetomidine group required adjunctive treatment, compared with 34 and 38 patients in the fentanyl and saline groups, respectively. Importantly, none of the patients treated with nebulized dexmedetomidine required an epidural blood patch. This finding was consistently reported across all included studies, suggesting that nebulized dexmedetomidine may reduce the need for escalation to invasive rescue therapies.

Adverse events were infrequently reported and were generally mild in nature. No serious treatment-related complications attributable to nebulized dexmedetomidine were identified. Collectively, these findings indicate that nebulized dexmedetomidine may not only improve symptom control but also decrease the reliance on supplementary analgesic interventions and invasive procedures such as EBP.

Adverse Events

Adverse events reported across the included studies were generally mild and self-limiting, comprising dry mouth, drowsiness, nausea, dizziness, bradycardia, and sedation (Table 4). Importantly, no serious adverse events attributable to nebulized dexmedetomidine were reported in any study. Furthermore, no treatment discontinuations due to adverse effects were described. Of note, three patients in the neostigmine/atropine group developed abdominal cramps, an adverse event that was not observed among patients receiving nebulized dexmedetomidine or other comparator interventions. [12] Overall, the available evidence suggests that nebulized dexmedetomidine is well tolerated and is associated with a favorable safety profile.

DISCUSSION

This systematic review aimed to evaluate the efficacy and safety of nebulized dexmedetomidine for the treatment of post-dural puncture headache (PDPH) in obstetric patients following neuraxial anesthesia or analgesia. The review included four randomized controlled trials and one case report describing two patients, providing the most up-to-date synthesis of the available evidence regarding this emerging therapeutic approach.

Across the included studies, nebulized dexmedetomidine was generally administered at a dose of 1 µg/kg diluted to a total volume of 4 mL and delivered via nebulization. In most studies, treatment was administered every 12 hours for up to three days or until symptom resolution. In contrast, the case report described successful symptom management following a single nebulized dose[2]. Despite variations in treatment duration, the findings consistently demonstrated a reduction in headache severity among patients receiving dexmedetomidine.

Pain intensity, assessed using the Visual Analog Scale (VAS), was the primary outcome in all studies. Compared with saline and fentanyl, nebulized dexmedetomidine was associated with significantly lower VAS scores at 24, 48, and 72 hours following treatment initiation. When compared with neostigmine/atropine, dexmedetomidine demonstrated comparable analgesic efficacy [12]. Collectively, these findings suggest that nebulized dexmedetomidine is more effective than placebo and fentanyl for PDPH management, while offering similar effectiveness to neostigmine/atropine. Furthermore, the rapid symptom improvement reported in the case report supports the potential for a relatively fast onset of therapeutic action.

The safety profile of nebulized dexmedetomidine was generally favorable. Reported adverse events were predominantly mild and included drowsiness, dry mouth, sedation, and occasional bradycardia. Importantly, no serious adverse events were reported across the included studies. Although dexmedetomidine was associated with a slightly higher incidence of sedation-related symptoms, patients receiving fentanyl more frequently experienced nausea and dizziness [9-12]. Similarly, participants treated with neostigmine/atropine reported adverse effects such as diarrhea, abdominal discomfort, muscle twitches, and abdominal cramps, which are consistent with the known cholinergic effects of neostigmine[12]. Overall, the available evidence suggests that nebulized dexmedetomidine is well tolerated and may offer a more favorable adverse-effect profile than several alternative pharmacologic treatments.

An important clinical finding was the reduced need for rescue therapies following dexmedetomidine administration. The requirement for epidural blood patch (EBP), widely regarded as the definitive treatment for refractory PDPH, was uncommon among patients receiving nebulized dexmedetomidine. In contrast, patients receiving saline or fentanyl more frequently required additional interventions, including oral paracetamol, caffeine, and other supportive therapies [9,11,12]. In the study comparing dexmedetomidine with neostigmine/atropine, only one patient in the comparator group required additional treatment, whereas none of the patients receiving dexmedetomidine required further intervention. These findings suggest that nebulized dexmedetomidine may effectively control symptoms and reduce the need for invasive procedures such as EBP.

The therapeutic effects of dexmedetomidine in PDPH are likely to be multifactorial. As a highly selective α_2-adrenergic receptor agonist, dexmedetomidine produces analgesic, sedative, and sympatholytic effects through inhibition of central nociceptive transmission. In addition, previous studies have demonstrated reductions in middle cerebral artery blood flow velocity and increases in pulsatility index following dexmedetomidine administration. These hemodynamic effects may contribute to symptom relief by attenuating the compensatory cerebral vasodilation believed to occur as a result of cerebrospinal fluid loss [11,12.] Consequently, dexmedetomidine may address both the pain pathways and cerebrovascular mechanisms implicated in the pathophysiology of PDPH.

The nebulized route offers several practical advantages over existing treatment modalities. It is non-invasive, simple to administer, and avoids the risks associated with repeat neuraxial procedures. Nebulized administration also bypasses first-pass hepatic metabolism and does not require intravenous access, making it convenient in both inpatient and outpatient settings. These attributes may be particularly beneficial in resource-limited environments where access to anesthesiology services and epidural blood patch procedures may be restricted.

CONCLUSION

This systematic review suggests that nebulized dexmedetomidine is a safe, effective, and well-tolerated treatment option for PDPH in obstetric patients. Compared with placebo and fentanyl, it appears to provide superior headache relief, faster symptom resolution, and a reduced requirement for rescue therapies, including epidural blood patch. Its efficacy appears comparable to that of neostigmine/atropine while maintaining a favorable safety profile. Although the current evidence is promising, the available studies are limited in number and sample size. Larger, high-quality, multicenter randomized controlled trials are required to confirm these findings and establish the role of nebulized dexmedetomidine in the routine management of PDPH.

LIMITATIONS

Several limitations should be considered when interpreting the findings of this review. First, the primary outcome measure used across the included studies was the Visual Analog Scale (VAS)[13], a subjective assessment tool that may not fully reflect clinically meaningful differences in pain severity. Although some studies reported secondary outcomes such as

rescue medication use and the requirement for epidural blood patch, future investigations should incorporate more objective and standardized outcome measures.

Second, the overall body of evidence remains limited, comprising only four randomized controlled trials and a single case report. Most studies were conducted in relatively small populations. Finally, dexmedetomidine is not currently approved for nebulized administration in North America and most available data are derived from European and Asian populations, its generalizability of these findings remains limited. Therefore, additional studies involving diverse patient populations are required before widespread clinical adoption can be recommended.

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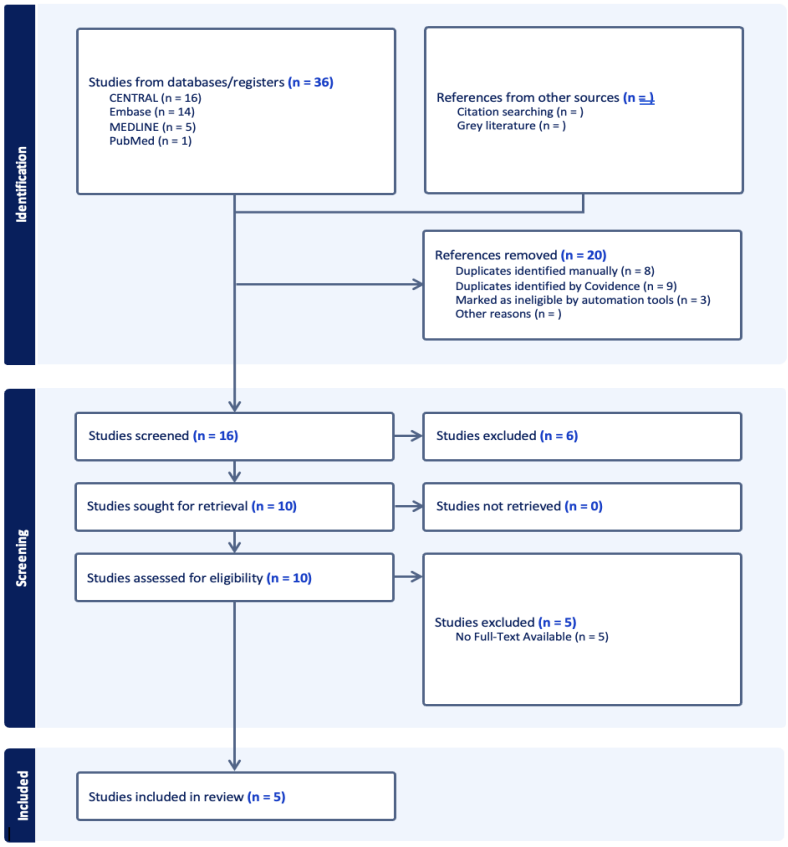

Figure 1: PRISMA flowchart. This chart showcases databases and studies screened, excluded and included in review.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Kumar et al. 2024	+	+	+	+	+	+	+
Soliman et al. 2023	+	+	+	+	+	+	+
Garg et al., 2024	+						
Mowafy et al. 2021	+	+	+	+	+	+	+

Interpretation: "+" = Low risk of bias,"–" = High risk of bias, "?" = Unclear risk of bias

Figure 2: Quality Assessment of Included Randomized Controlled Trials

Table 1: Demographics

Study	Country	Patients	Age (yrs)	BMI	Weight (Kg)	ASA status
Kumar et al. 2024	India	90/90	25.03–26.60		52.23–53.93	2
Soliman et al. 2023	Egypt	90/90	28.77±5.23	28.84±2.30	30.98±2.68	2
Garg et al. 2024	India	65/65	28.7–29.4			
Mowafy et al. 2021	Egypt	44/43	26.5–27	25.8–26.3		2
Thomas et al. 2025	USA	0/2	27	31.37		2

Table 2: Interventions

Study	Study type	Procedure	Drug/Procedure	Dose/Duration	Comparator(s)
Kumar et al. 2024	RCT	LSCS under spinal	Nebulized Dexmedetomidine	1 µg/kg BID x 3 days	Fentanyl; Saline
Soliman et al. 2023	RCT	LSCS under spinal	Nebulized Dexmedetomidine	1 µg/kg BID x 3 days	Neostigmine/Atropine; Saline
Garg et al., 2024	RCT	LSCS under spinal	Nebulized Dexmedetomidine	*Not mentioned in the final manuscript	Fentanyl
Mowafy et al. 2021	RCT	LSCS under spinal	Nebulized Dexmedetomidine	1 µg/kg BID x 3 days OR VAS ≤3 and Lybecker classification score <2	Saline
Thomas et al. 2025	Case Report	One patient had LSCS under spinal Second patient had epidural	Nebulized Dexmedetomidine	1 µg/kg single dose	NA

Table 3: Primary Outcome (VAS). VAS score across studies (reported as median (IQR), mean±SD). T0 represents baseline VAS scores before the administration of dexmedetomidine. T1 indicates VAS scores at 24 hours post-administration, T2 denotes VAS scores at 48 hours post-administration, and T3 signifies VAS scores at 72 hours post-administration. D-dexmeditomidine, F- Fentanyl, S- Saline, N- Neostigmine

Study	Group	n	T0	T1	T2	T3
Kumar et al. 2024	D	30	7 (2)	2 (1)	2 (1)	1 (1)
	F	30	7 (2)	3.5 (4)	3 (2)	3 (4)
	S	30	7 (2)	4 (2.5)	3 (2)	3.5 (4)
Soliman et al. 2023	D	30	7 (5-8)	1 (0-1)	0 (0-0.25)	0 (0-0)
	S	30	6 (5-7.25)	2 (1-5.25)	1 (0-6)	0 (0-2)
	N	30	6 (5-7.25)	1 (0-2)	0 (0-1)	0 (0-0)
Garg et al., 2024	D	32	6.8±1.2	3.1 ±1.4	2.0±1.1	1.2±0.8
	F	33	7.0 ±1.1	4.5 ±1.3	3.4±1.2	2.8±1.1
Mowafy et al. 2021	D	21	7.07	3.52	1.85	1.23
	S	22	6.95	5.81	4.86	3.72
Thomas et al. 2025	D	2	8.5	NR	NR	NR

Table 4: Secondary outcomes. These included adverse outcomes and need for additional treatments. *p<0.05

Study	Group	Adverse effects	Use of additional treatment (including oral paracetamol, oral caffeine, and EBP)	EBP Only
Kumar et al. 2024	D	Dry mouth (2)	6*	0
	F	Dry mouth (1)	34*	0
	S	Dry mouth (1)	38*	0
Soliman et al., 2023	D	Bradycardia (1)	0*	0
	S	Nil	7*	7
	N	Diarrhea (1)	1*	1
		Abdominal cramps (3) *		
		Muscle twitches (1)		
Garg et al., 2024	D	Drowsiness (12)	NR	NR
		Dry mouth (10)		
		Nausea (2)		
		Dizziness (1)		
	F	Drowsiness (8)	NR	NR
		Nausea (11)		
		Dizziness (9)		
Mowafy et al. 2021	D	Hypotension (0)	0	0
		Bradycardia (1)		
		Sedation (1)		
	S	Hypotension (0)	2	2
		Bradycardia (0)		
		Sedation (0)		
Thomas et al. 2025	D	NR	NR	NR