Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 09, 2024

Original Research Paper

COMPARISON OF NEBULIZED DEXMEDETOMIDINE TO FENTANYL IN TREATING POST-DURAL PUNCTURE HEADACHE IN SUBJECTS FOLLOWING CESAREAN SECTION UNDER SPINAL ANESTHESIA

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ABSTRACT

Background: PDPH or post-dural puncture headache shows an incidence of nearly 0.5% to 2% after spinal anesthesia in obstetric subjects. Various treatment modalities used for managing PDPH include epidural blood patches, non-steroidal anti-inflammatory drugs, paracetamol, caffeine, bed rest, hydration, and others.

Aim: The present study aimed to comparatively assess the nebulized dexmedetomidine to fentanyl in treating PDPH post-dural puncture headache in subjects following cesarean section under spinal anesthesia.

Methods: 180 obstetric subjects with ASA II/III and aged 18-35 years with PDPH were assessed. Subjects were divided into three groups where Group I subjects were given 1µg/kg dexmedetomidine nebulization, group II subjects were given 1 µg/kg fentanyl nebulization and Group III subjects were given 4mL saline nebulization. Nebulization was done for 12 hourly for 72 hours. Parameters assessed were pain score and additional treatment need as epidural blood patch, caffeine, and paracetamol.

Results: The study results showed that pain scores at 1, 6, 12, 24, 48, and 72 hours after nebulization were significantly lower in Group I compared to Group II and Group III with a p-value of <0.001. The number of subjects needing additional analgesic therapy was lesser in Group I compared to Group II and Group III with a p-value of <0.001.

Conclusions: The present study concludes that nebulization with dexmedetomidine results in an effective decrease in pain scores and symptoms of PDPH. Nebulization with fentanyl does not eliminate the symptoms of PDPH in comparison to the control group.

Keywords: PDPH, nebulization, dexmedetomidine, fentanyl, epidural blood patch

INTRODUCTION

PDPH (post-dural puncture headache) is a debilitating and potential complication associated with spinal anesthesia in pregnant females undergoing cesarean section and has been reported to have an incidence of 0.5% to 2%. The cause of PDPH is not known completely known. Various existing theories suggest that the main etiological factor for loss of cerebrospinal fluid via dural tears leads to traction on reflex vasodilation and pain-sensitive intracranial structures. Different methods used for managing PDPH include the use of NSAIDs (non-steroidal anti-inflammatory drugs), paracetamol, caffeine, maintenance of supine posture, and proper hydration, etc.[1]

Dexmedetomidine is a highly selective and centrally acting α-2 agonist having anti-sialogogue, sympatholytic, anxiolytic, analgesic, and hypnotic actions. These α-2 receptors are seen in large quantity in substantia gelatinosa of the locus coeruleus and dorsal horn area, both of which are nociceptive transmission modulators. The role of nebulized dexmedetomidine has been well-explained in pediatric premedication during minor dental procedures as an analgesic and anxiolytic agent and for the treatment of PDPH and bronchoscopy.[2]

Dexmedetomidine depicts high bioavailability of nearly 65% via nasal mucosa and 82% via buccal mucosa. Dexmedetomidine shows cerebral vasoconstriction, sympatholysis, analgesia, and anxiolysis as large concentrations of these α-2 receptors are seen in large quantities in substantia gelatinosa of the locus coeruleus and vascular smooth vessels. This can help in understanding the mechanism of action in PDPH. New routes of administering fentanyl including inhalational and intranasal routes have been utilized successfully for pain relief in different surgeries. Existing literature data suggest that nebulized fentanyl is as productive as intravenous fentanyl in management of the acute pain.[3,4]

The present study hypothesized that nebulized dexmedetomidine will result in better analgesia in comparison to nebulized fentanyl or placebo drugs in the management of postpartum PDPH with no significant increase in adverse events. The present study aimed to comparatively assess the nebulized dexmedetomidine to fentanyl in treating PDPH post-dural puncture headache in subjects following cesarean section under spinal anesthesia.

MATERIALS AND METHODS

The present randomized-controlled clinical study was aimed to comparatively assess the nebulized dexmedetomidine to fentanyl in treating PDPH post-dural puncture headache in subjects following cesarean section under spinal anesthesia. The study was done at Department of Anesthesiology, RSDKS Government Medical College, Ambikapur, Surguja, Chhattisgarh after the clearance was given by the concerned Institutional Ethical committee. The study subjects were from the Department of Obstetrics and Gynecology of the Institute. Verbal and written informed consent were taken from all the subjects before study participation.

The study assessed 180 subjects with PDPH. The inclusion criteria for the study were subjects in ASA (American Society of Anesthesiologists) status II/III, in the age range of 18-35 years, who were willing to participate in the study, and subjects that qualified the PDPH criteria as per International Headache Society[5] with headache severity scores of >4. The exclusion criteria for the study were subjects having bradyarrhythmia, hemodynamic instability, chronic treatment of headache, other type

of headache, history of migraine, epileptic subjects, asthmatic subjects, subjects allergic to fentanyl or dexmedetomidine, uncooperative subjects, unconscious subjects, subjects with BMI >24kg/m2, and subjects that did not give consent for study participation. All the subjects were evaluated for headache severity using NRS (numerical rating scale) on scores of 0-10 where 0 showed no pain and 10 depicted worst pain. Subjects were also enquired about the headache medication taken before study enrolment.

Included subjects were randomly divided into three groups where Group I subjects were given 1µg/kg dexmedetomidine nebulization, group II subjects were given 1 µg/kg fentanyl nebulization, and Group III subjects were given 4mL saline nebulization. Nebulization was done for 12 hourly for 72 hours using a compressor nebulizer in a semi-recumbent position. In all three groups, volume was kept constant at 4mL. The necessary drug for nebulization was loaded by a person blinded to the study duration. Subjects were unaware of the drug being given to them. Before starting nebulization, baseline vitals including non-invasive blood pressure, oxygen saturation, and heart rate were recorded.

Headache severity scores using NRS were assessed by anesthesiologists unaware of the study group at baseline, during nebulization, after nebulization, and at 1, 6, 12, 24, 48, and 72 hours. Subjects were asked to report pain after 15 minutes of upright sitting. In subjects with NRS >4 even after 1 hour, oral 650 mg PCM (paracetamol) was given. Oral 300mg caffeine was given once daily to subjects that did not respond to paracetamol in an hour. In subjects where PPDH was not relieved even after 72 hours and NRS was >4, an autologous blood patch was used. In subjects where a target NRS of <4 was gained, nebulization with saline was done to maintain the blinding.

The main outcome in the study subjects was headache severity assessed with NRS after 24 hours of nebulization. The secondary outcome assessed was several subjects needing additional analgesics such as caffeine paracetamol or an epidural blood patch. The study also assessed sedation (modified Ramsay sedation scale >3) by using a five-point scale (sedation score (SS) 1 = Agitated, 2 = Alert, 3 = Calm, 4 = Drowsy, 5 = Asleep) at baseline, after first nebulization, and every 4 hours till 72 hours. Adverse effects noted in study subjects included coughing and sneezing after and during nebulization, dry mouth, oxygen desaturation, bradycardia, and hypotension, and were managed with atropine and mephentermine administration and oxygen supplementation using the face mask.

The data gathered were analyzed statistically using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) for assessment of descriptive measures, one-way ANOVA (analysis of variance), Kruskal–Wallis test, and chi-square test. The results were expressed as mean and standard deviation and frequency and percentages. The p-value of <0.05 was considered statistically significant.

RESULTS

The present randomized-controlled clinical study was aimed to comparatively assess the nebulized dexmedetomidine to fentanyl in treating PDPH post-dural puncture headache in subjects following cesarean section under spinal anesthesia. The present study assessed 180 obstetric subjects with ASA II/III aged 18-35 years with PDPH were assessed. Subjects were divided into three groups where

Group I subjects were given 1µg/kg dexmedetomidine nebulization, group II subjects were given 1 µg/kg fentanyl nebulization and Group III subjects were given 4mL saline nebulization.

The mean age of the study subjects was 26.60±4.73, 25.01±3.63, and 26.31±3.77 years respectively which was statistically non-significant with p=0.288. The mean weight of study subjects was 53.91±10.69, 53.74±9.58, and 52.21±8.75 kg respectively showing statistical non-significance with p=0.755. ASA status I and II were statistically comparable in three groups with p=0.262. The number of attempts as 1st, 2nd, and >2 attempts were comparable in three groups with p=0.425, 0.781, and 0.452 respectively. Surgery duration was 80.81±24.33, 83.14±25.01, and 83.21±24.86 minutes respectively which was statistically non-significant with p=0.931 (Table 1).

The study results showed that assessing NRS at different time intervals in three groups of study subjects was statistically non-significant in three groups at 0 hours with p=0.852. However, a highly statistically significant difference was seen among the three groups with the highest values for Group III followed by Group II and I after nebulization, 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours with p<0.001 at each time interval (Table 2).

It was seen that the number of subjects needing additional supplements for PDPH, hypotension, bradycardia, and Ramsay sedation score of >2 were seen in no study subject from any group. The adverse event of dry mouth was seen in 7% (n=4), 3% (n=2), and 3% (n=2) study subjects from Group I, II, and III respectively which was statistically non-significant with p=0.767. The epidural blood patch was needed in no study subject from any group. Oral caffeine need was significantly higher in Group III with 33% (n=20) study subjects followed by 27% (n=16) study subjects from Group II and 7% (n=4) study subjects from Group I with p=0.03. Oral paracetamol was needed by 93% (n=56) subjects from Group III which was significantly higher compared to Group II where it was needed in 87% (n=52) subjects, and least in 13% (n=8) study subjects respectively with p<0.001 (Table 3).

DISCUSSION

The present study assessed 180 obstetric subjects with ASA II/III aged 18-35 years with PDPH were assessed. Subjects were divided into three groups where Group I subjects were given 1µg/kg dexmedetomidine nebulization, group II subjects were given 1 µg/kg fentanyl nebulization and Group III subjects were given 4mL saline nebulization. The design of the present study was similar to the studies of Kumar NRR et al[6] in 2020 and Root-Bernstein R et al[7] in 2019 where a study design similar to the present study was adopted by the authors in their respective study subjects having PDPH.

Concerning demographic data, the mean age of the study subjects was 26.60±4.73, 25.01±3.63, and 26.31±3.77 years respectively which was statistically non-significant with p=0.288. The mean weight of study subjects was 53.91±10.69, 53.74±9.58, and 52.21±8.75 kg respectively showing statistical non-significance with p=0.755. ASA status I and II were statistically comparable in three groups with p=0.262. The number of attempts as 1st, 2nd, and >2 attempts were comparable in three groups with p=0.425, 0.781, and 0.452 respectively. Surgery duration was 80.81±24.33, 83.14±25.01, and 83.21±24.86 minutes respectively which was statistically non-significant with p=0.931. These data were comparable to the findings of Kumari P et al[8] in 2021 and Abd El-Hamid AM et al[9] in 2015

where demographic data reported by the authors in their studies was comparable to the reporting of the present study.

It was seen that on assessing NRS at different time intervals in three groups of study subjects, it was statistically non-significant in three groups at 0 hours with p=0.852. However, a highly statistically significant difference was seen among the three groups with the highest values for Group III followed by Group II and I after nebulization, 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours with p<0.001 at each time interval. These findings were consistent with the studies of Li A et al[10] in 2018 and Yoo H et al[11] in 2015 where numeric rating scales for pain recordings similar to the present study were reported by the authors in their respective studies.

The study results showed that concerning the number of subjects needing additional supplements for PDPH, hypotension, bradycardia, and Ramsay sedation score of >2 were seen in no study subject from any group. The adverse event as the dry mouth was seen in 7% (n=4), 3% (n=2), and 3% (n=2) study subjects from Groups I, II, and III respectively which was statistically non-significant with p=0.767. The epidural blood patch was needed in no study subject from any group. Oral caffeine need was significantly higher in Group III with 33% (n=20) study subjects followed by 27% (n=16) study subjects from Group II and 7% (n=4) study subjects from Group I with p=0.03. Oral paracetamol was needed by 93% (n=56) subjects from Group III which was significantly higher compared to Group II where it was needed in 87% (n=52) subjects, and least in 13% (n=8) study subjects respectively with p<0.001. These results were in agreement with the findings of Kumar A et al[12] in 2019 and Mowafy SMS et al[13] in 2021 where authors reported a similar need for additional supplements in their study subjects as seen in the present study.

CONCLUSIONS

Considering its limitations, the present study concludes that nebulization with dexmedetomidine results in an effective decrease in pain scores and symptoms of PDPH. Nebulization with fentanyl does not eliminate the symptoms of PDPH in comparison to the control group.

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TABLES

Characteristics	**Group I (n=60)**	**Group II (n=60)**	**Group III (n=60)**	**p-value**
Mean age (years)	26.60±4.73	25.01±3.63	26.31±3.77	0.288
Weight (kg)	53.91±10.69	53.74±9.58	52.21±8.75	0.755
ASA status				
I	56	48	54	0.262
II	4	12	6	
Number of Attempts				
1st attempt spinal	44	48	40	0.425
2nd attempt spinal	8	6	10	0.781
>2 attempts spinal	4	6	10	0.452
Surgery duration (mins)	80.81±24.33	83.14±25.01	83.21±24.86	0.931

Table 1: Demographic and disease data in the study subjects

S. No	**Time**	**Group I**	**Group II**	**Group III**	**p-value**

1.	**0 hour**	7 (5.48-7.34)	7 (6.43-7.25)	7 (6.33-7.14)	0.852
2.	**After nebulization**	1.5 (1.41-2.07)	6 (5.41-6.46)	6 (5.46-6.56)	<0.001
3.	**1 hour**	1.5 (1.42-2.13)	6 (4.79-6.23)	6 (5.22-6.39)	<0.001
4.	**6 hours**	2 (1.56-2.23)	5 (4.66-5.96)	5 (4.54-5.74)	<0.001
5.	**12 hours**	2 (1.43-2.04)	3.5 (3.15-4.66)	3.5 (3.30-4.97)	<0.001
6.	**24 hours**	2 (1.42-2.04)	3.5 (3.15-4.66)	4 (3.33-4.59)	<0.001
7.	**48 hours**	2 (1.38-1.89)	3 (2.33-3.48)	3 (2.34-3.67)	<0.001
8.	**72 hours**	1 (1.26-1.81)	3 (2.86-4.42)	3.5 (3.09-4.52)	<0.001

Table 2: NRS at different time intervals in three groups of study subjects

S. No	Parameters	Group I	Group II	Group III	p-value
1.	**Hypotension/bradycardia**	0	0	0	
2.	**Ramsay sedation score >2**	0	0	0	
3.	**Adverse event (dry mouth)**	4 (7)	2 (3)	2 (3)	0.767
4.	**Epidural blood patch**	0	0	0	
5.	**Oral caffeine**	4 (7)	16 (27)	20 (33)	0.03
6.	**Oral paracetamol**	8 (13)	52 (87)	56 (93)	<0.001

Table 3: Number of subjects needing additional supplements for PDPH