Original Article

Comparative evaluation of nebulised dexmedetomidine vs fentanyl for the treatment of post-dural puncture headache (PDPH) in parturients after caesarean section under spinal anaesthesia: A randomised controlled study

Address for correspondence:
Dr. Chandni Sinha, Room No. 502, B-Block, OT Complex, AIIMS, Patna, Bihar, India.
E-mail: Chandni.doc@gmail.com

Submitted: 17-Aug-2023
Revised: 17-Oct-2023
Accepted: 24-Oct-2023
Published: 29-Jan-2024

Access this article online

Website: https://journals.lww.com/ijaweb

DOI: 10.4103/ija.ija_789_23

Quick response code

Amarjeet Kumar, Chandni Sinha, Kunal Singh, Monika Anant[1], Ajeet Kumar, Poonam Kumari

Departments of Anaesthesiology and [1]Obstetrics and Gynaecology, All India Institute of Medical Sciences, Patna, Bihar, India

ABSTRACT

Background and Aims: The incidence of post-dural puncture headache (PDPH) following spinal anaesthesia in the obstetric population is around 0.5%–2%. Hydration, bed rest, caffeine, paracetamol, non-steroid anti-inflammatory drugs, epidural blood patches, etc., are the various modalities used for its management. This study aims to compare nebulised dexmedetomidine versus fentanyl for the treatment of PDPH in parturients after caesarean section under spinal anaesthesia. **Methods:** Ninety obstetric patients aged 18–35 years with American Society of Anesthesiologists (ASA) physical status II/III and suffering from PDPH as per the criteria of the International Headache Society after caesarean section under spinal anaesthesia were recruited in this double-blinded randomised study. Patients were randomised to Group D (dexmedetomidine 1 μg/kg nebulisation), Group F (fentanyl 1 μg/kg nebulisation), and Group S (saline nebulisation 4mL). The nebulisation was done 12 hourly for 72 hours. Assessment parameters included pain score and the requirement of additional treatment such as paracetamol, caffeine, and epidural blood patch. Analysis of variance test was used for continuous quantitative variables, and the Kruskal–Wallis test was used for quantitative discrete data. **Results:** The pain scores at 1, 6, 12, 24, 48, and 72 hours following nebulisation were significantly lower in Group D in comparison to groups F and S ($P < 0.001$). The number of patients requiring additional analgesic therapy was lower in Group D in comparison to patients in other groups ($P < 0.001$). **Conclusion:** Dexmedetomidine nebulisation resulted in effective reduction in PDPH symptoms and pain scores. Nebulisation with fentanyl did not alleviate PDPH symptoms when compared to the control group.

Keywords: Caesarean section, dexmedetomidine, fentanyl, nebulisation, obstetric anaesthesia, PDPH, post-dural puncture headache, spinal anaesthesia

INTRODUCTION

Post-dural puncture headache (PDPH) is a potential and debilitating complication of spinal anaesthesia in pregnant patients undergoing caesarean sections, with a reported incidence of 0.5%–2%.[1] The cause of PDPH is not completely elucidated. Theories suggest that the primary cause is the loss of cerebrospinal fluid through dural tears, resulting in traction on pain-sensitive

How to cite this article: Kumar A, Sinha C, Singh K, Anant M, Kumar A, Kumari P. Comparative evaluation of nebulised dexmedetomidine vs fentanyl for the treatment of post-dural puncture headache (PDPH) in parturients after caesarean section under spinal anaesthesia: A randomised controlled study. Indian J Anaesth 2024;68:159-64.

intracranial structures and reflex vasodilation. Various methods for management include proper hydration, maintaining a supine posture, caffeine, paracetamol, nonsteroid anti-inflammatory drugs (NSAID), etc.[2]

Dexmedetomidine is a highly selective, centrally acting α-2 agonist with hypnotic, analgesic, anxiolytic, sympatholytic, and anti-sialogogue effects. These α-2 receptors are present in abundance in the substantia gelatinosa of the dorsal horn and locus coeruleus area, both of which are nociceptive transmission modulators. The role of nebulised dexmedetomidine has been established in paediatric premedication, in minor dental procedures as anxiolytic and analgesic, and bronchoscopy and the treatment of PDPH.[3,4] Dexmedetomidine a high bioavailability through nasal mucosa (65%) and buccal mucosa (82%).[5] α-2 receptors are found in large concentrations in locus coeruleus and vascular smooth vessels. Hence, it produces anxiolysis, analgesia, sympatholysis, and cerebral vasoconstriction.[6] This could explain the mechanism of its action in PDPH. Newer routes of fentanyl administration, intranasal and inhalational, have been successfully used for pain relief in various surgeries. Evidence suggests that nebulised fentanyl is as effective as intravenous fentanyl in the management of acute pain.[7,8]

We hypothesised that nebulised dexmedetomidine would provide better analgesia than nebulised fentanyl or placebo for the treatment of postpartum PDPH with no increase in adverse effects. Hence, this study aimed to compare nebulised dexmedetomidine versus fentanyl for the treatment of PDPH in parturients undergoing caesarean section under spinal anaesthesia.

METHODS

Following approval by the institutional ethics committee (vide approval number AIIMS/Pat/IEC/2019/391; dated 17 September 2019) and registration at the Clinical Trials Registry-India (vide registration number CTRI/2019/11/022184; https://ctri.nic.in/), this double-blind, randomised controlled study was conducted in a tertiary care centre between December 2019 and May 2023. Ninety obstetric patients aged 18–35 years with American Society of Anesthesiologists (ASA) physical status II/III and qualifying for the criteria for PDPH (with headache severity score >4) as laid down by the International Headache Society[9] were recruited into the study. The study was carried out according to the principles of the Declaration of Helsinki, 2013. After explaining the details of the study procedure, written informed consent was obtained for participation in the study and the use of the patient data for research and educational purposes. Exclusion criteria were body mass index >24 kg/m^2, unconscious and uncooperative patients, inability to obtain informed consent, allergic to dexmedetomidine/fentanyl, asthmatics, epileptics, patients with a history of migraine, other types of headache, on chronic treatment of headache, haemodynamic instability, or bradyarrhythmia. Patients were assessed for headache severity by using the numerical rating scale (NRS) (NRS 0 = No pain, NRS 10 = Worst pain) and medication taken for headache prior to their enrolment into the study.

Block randomisation was performed using online software (Open Epi software version 3.01, Atlanta, GA, USA). The random allocation sequence was concealed in sequentially numbered opaque, sealed envelopes, which were opened just before the intervention. Patients were allocated to one of the three groups by computer-generated random numbers: Group D – dexmedetomidine 1 μg/kg nebulisation, Group F – fentanyl 1 μg/kg nebulisation, and Group S – saline nebulisation (4 mL). The nebulisation was done 12 hourly for 72 hours in a semi-recumbent position by using a compressor nebuliser (Philips Respironics Innospire Essence Nebuliser; Tangmere Chichester PO20 2FT UK). The volume of all three groups was kept constant at 4 mL. A pharmacist who was not involved in the collection or analysis of the data loaded the necessary drug for nebulisation. Patients were unaware of the drug being given to them. Before the start of the nebulisation, a monitor (Philips Goldway GS20 Patient Monitor; Nanshan, Shenzhen, China) was connected, and baseline vitals such as heart rate, oxygen saturation, and non-invasive blood pressure measurements were taken.

An anaesthesiologist blinded to study group allocation assessed headache severity by using NRS (NRS 0 = No pain, NRS 10 = Worst pain) at baseline, during nebulisation, after nebulisation, and at 1, 6, 12, 24, 48, and 72 hours. The patients were asked to report pain after 15 minutes of sitting upright. If NRS was more than 4 even after 1 hour, oral paracetamol (PCM) 650 mg was administered. Oral caffeine 300 mg once a day was given to the patients who did not respond to paracetamol in an hour. An autologous blood patch was planned if PDPH was not relieved (NRS >4) even after 72 hours. For patients in whom the target

NRS (NRS <4) was achieved, subsequent nebulisation with saline was done to maintain blinding.

The primary outcome of this study was the headache severity as measured using NRS at 24 hours after the first nebulisation. The secondary outcome was the number of patients requiring additional analgesics (paracetamol, caffeine) or an epidural blood patch. We also recorded 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 nebulisation, and every 4 hours till 72 hours. Adverse effects such as hypotension, bradycardia, oxygen desaturation, dry mouth, and sneezing and coughing during and after nebulisation were also recorded and managed by intravenous mephentermine and atropine administration and oxygen supplementation using face mask.

At the time of conception of the study, no other studies compared the analgesic effect of dexmedetomidine nebulisation with fentanyl nebulisation in patients having PDPH. For sample size calculation, we conducted a pilot study on five patients with PDPH who reported a mean [standard deviation (SD)] pain score of 3.2 (0.83) 24 hours after dexmedetomidine nebulisation. Expecting dexmedetomidine nebulisation to be better than fentanyl, anticipated NRS scores would be 20% more in the fentanyl group. With a power of 80% and an alpha error of 0.05, the sample size was 26 in each group. Taking a drop out of 10%, 30 patients in each group were recruited.

Data analysis was done using statistical package for social sciences (SPSS version 22.0 released 2013. Armonk, New York: International Business Machines Corporation). Continuous quantitative normally distributed data (age, weight, and duration of surgery) are presented as mean (SD), [95% confidence interval (CI)] and were compared using analysis of variance (ANOVA). Quantitative discrete data (NRS score) are expressed as median [inter quartile range (IQR)] and 95% CI. It was compared using the Kruskal–Wallis test. The Chi-square test was used for comparisons of categorical variables (number of patients requiring additional analgesics), which was expressed as proportions (%). *P* values <0.05 were considered to be statistically significant.

RESULTS

Ninety patients were randomly allocated into three groups and completed the study protocol [Figure 1]. In total, 1917 parturients underwent elective caesarean section during the study period of three and half years, out of which 1652 (86.2%) received spinal anaesthesia and the rest (13.8%) received general anaesthesia. One hundred and two (6.2%) postpartum females developed PDPH and were enroled in this study. Eight patients did not meet the inclusion criteria (four patients were taking analgesics for chronic headaches, two patients had a history of asthma, and one patient was on antiepileptic drugs), and four patients refused to participate in the study. There was no difference in demographic parameters among the study groups [Table 1]. In addition, no statistically significant difference was found among the groups in terms of spinal attempts taken and duration of surgery [Table 1]. The baseline NRS score was comparable in the three groups. The pain scores after completion of the first nebulisation and at 1, 6, 12, 24, 48, and 72 hours following nebulisation were significantly lower in Group D in comparison to the other groups ($P < 0.001$) [Table 2]. There were no significant differences in pain scores between Group F and Group S most of the time ($P > 0.05$). The number of patients requiring additional analgesics (paracetamol and caffeine) after the first nebulisation was significantly lower in Group D in comparison to patients of other groups ($P < 0.001$) [Table 3]. However, there were almost equal numbers of patients who required additional analgesics (paracetamol or caffeine) in both fentanyl and control groups [Table 3]. In our study, none of the patients required an epidural blood patch. No significant major adverse effects were noted during nebulisation in patients of either group. Two patients of Group D and one patient, each of Group F and Group S, complained about dry mouth following nebulisation.

DISCUSSION

We observed a decrease in headache severity as assessed using NRS in patients with PDPH after dexmedetomidine nebulisation compared to fentanyl nebulisation and the control group. Nebulisation with fentanyl was not effective in controlling the symptoms compared to the control group.

The higher incidence of PDPH (6.2%) in postpartum females at our centre was due to the use of a dura-cutting needle.

The gold-standard epidural blood patch is invasive and causes complications such as seizures and

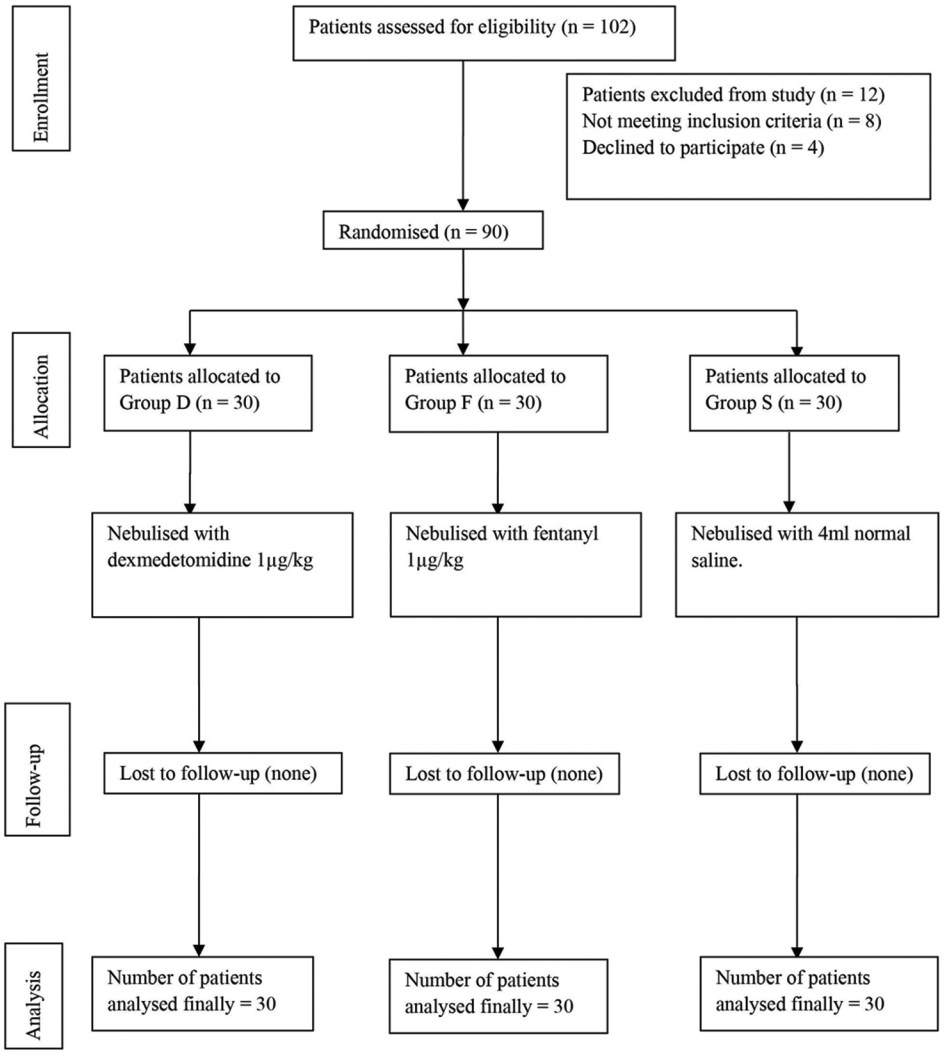

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Table 1: Demographic characteristics of the study population

Variables	Group D (*n*=30)	Group F (*n*=30)	Group S (*n*=30)	*P*
Age (years)	26.60 (4.75)	25.03 (3.65)	26.33 (3.79)	0.290
Weight (kg)	53.93 (10.71)	53.76 (9.60)	52.23 (8.77)	0.757
American Society of Anesthesiologists physical status (II/III)	28/2	24/6	27/3	0.260
Number of patients				
1st attempt spinal	22	24	20	0.427
2nd attempt spinal	4	3	5	0.783
>2 attempt spinal	2	3	5	0.454
Duration of surgery (minutes)	80.83 (24.35)	83.16 (25.03)	82.33 (24.88)	0.933

Data expressed as mean (standard deviation) or frequency. D=Dexmedetomidine, F=Fentanyl, S=Saline

meningitis.[10,11] Hence, the quest for an ideal non-invasive pharmacological technique remains. Mowafy and Ellatif[12] found encouraging results in their study in which they compared nebulisation with 1 µg/kg dexmedetomidine to saline in post-caesarean patients with PDPH. The patients were symptomatically better after dexmedetomidine nebulisation. Transcranial Doppler (TCD) showed a reduction in the mean flow velocity of the middle cerebral artery due to its vasoconstrictive effect.[12] This decrease in arterial flow velocity has been previously demonstrated in healthy volunteers in a study done by Drummond *et al*.[13]

We chose a dose of 1 µg/kg based on our previous experience with five PDPH patients, where the

therapeutic effect was achieved with no adverse effects.[14] The plasma concentration required to achieve therapeutic effect in adults is 200–400 pg/mL.[15] Studies have shown that 1 μg/kg through nasal atomisation or nasal route achieves this level.[15,16]

Fentanyl is a highly potent lipophilic opioid with good trans-nasal bioavailability. Nebulised fentanyl in the dose of 4 μg/kg has been used for post-operative pain management.[6,17] A lower dose of 2 μg/kg has been used to facilitate bronchoscopy.[18] The possible mechanism of its analgesic effect in PDPH patients would be due to its local action on sphenopalatine ganglion and its systemic effect because of its absorption through the mucosa. Our study failed to demonstrate any effect of fentanyl on the reduction of symptoms of PDPH, which could be explained by the lower dose of 1 μg/kg. Both dexmedetomidine and fentanyl can act either on receptor or α 2A receptors to produce its peripheral effect. Root-Bernstein *et al*.[19] observed functional interactions between adrenergic and opioid receptors and synergistic action of opioid and α2-adrenoceptor agonists when co-administered.

The nebulisation route was used in this trial to avoid nasal irritation, cough, vocal cord irritation, and laryngospasm. Furthermore, it is preferred over the intravenous route to circumvent the adverse effects of bradycardia, hypotension, and respiratory depression, which occur when dexmedetomidine or fentanyl is administered as an intravenous bolus.[20]

There are a few limitations to this study. Pain scores are a subjective way to assess pain relief. The use of the Lybecker score would have been better as it assesses the functional restriction due to PDPH. The use of TCD would have evaluated the mean velocity of the middle cerebral artery but was not done due to its unavailability in our institute. We included only postpartum female patients, who are subjected to physiological changes of pregnancy and puerperium. Whether in non-pregnant female or male patients, these results can be extrapolated need to be studied.

Table 2: Numerical rating score (NRS) at different time points

Time interval	Group D (*n*=30)	Group F (*n*=30)	Group S (*n*=30)	*P*
0 h	7 (2) (6.50–7.36)	7 (2) (6.45–7.27)	7 (2) (6.35–7.16)	0.854
After nebulisation	1.5 (1) (1.43–2.09)	6 (2) (5.43–6.48)	6 (2) (5.48–6.58)	<0.001
1 h	1.5 (1) (1.44–2.15)	6 (3) (4.81–6.25)	6 (3) (5.24–6.41)	<0.001
6 h	2 (1) (1.58–2.21)	5 (3) (4.68–5.98)	5 (2) (4.56–5.76)	<0.001
12 h	2 (1) (1.45–2.06)	3.5 (4.25) (3.26–5.00)	3.5 (4.25) (3.32–4.99)	<0.001
24 h	2 (1) (1.44–2.02)	3.5 (4) (3.17–4.68)	4 (2.5) (3.31–4.61)	<0.001
48 h	2 (1) (1.40–1.91)	3 (2) (2.35–3.50)	3 (2.25) (2.36–3.69)	<0.001
72 h	1 (1) (1.28–1.83)	3 (4) (2.88–4.44)	3.5 (4) (3.11–4.54)	<0.001

Data expressed as median (interquartile range) (95% confidence interval). D=Dexmedetomidine, F=Fentanyl, S=Saline

CONCLUSION

Dexmedetomidine nebulisation resulted in an effective reduction in PDPH symptoms and pain scores. Nebulisation with fentanyl did not reach statistcal level of evidence to alleviate PDPH symptoms when compared to the control group.

Study data availability

De-identified data may be requested with reasonable justification from the authors (e-mail to the corresponding author) and shall be shared after approval as per the authors' institution policy.

Financial support and sponsorship

Nil.

Table 3: Number of patients requiring additional supplementary therapy for post-dural puncture headache

Variables	Group D (*n*=30)	Group F (*n*=30)	Group S (*n*=30)	*P*
Oral paracetamol	4 (13%) (3–30)	26 (87%) (69–96)	28 (93%) (78–99)	<0.001
Oral Caffeine	2 (7%) (1–22)	8 (27%) (12–45)	10 (33%) (17–52)	0.035
Epidural blood patch	0	0	0	-
Adverse event (dry mouth)	2 (7%) (1–22)	1 (3%) (0–17)	1 (3%) (0–17)	0.769
Ramsay sedation score >2	0	0	0	-
Hypotension/bradycardia	0	0	0	-

Data expressed as frequency (percentage) (95% confidence interval). D=Dexmedetomidine, F=Fentanyl, S=Saline

Conflicts of interest

There are no conflicts of interest.

ORCID:

Amarjeet Kumar: https://orcid.org/0000-0002-4272-5750

Chandni Sinha: https://orcid.org/0000-0002-4107-2671

Kunal Singh: https://orcid.org/0000-0003-4485-8757

Monika Anant: https://orcid.org/0000-0001-7957-379X

Ajeet Kumar: https://orcid.org/0000-0002-1464-6684

Poonam Kumari: https://orcid.org/0000-0003-0118-2187

REFERENCES

1. Sachs A, Smiley R. Post-dural puncture headache: The worst common complication in obstetric anaesthesia. Semin Perinatol 2014;38:386-94.
2. Russell R, Laxton C, Lucas DN, Niewiarowski J, Scrutton M, Stocks G. Treatment of obstetric post-dural puncture headache. Part 1: Conservative and pharmacological management. Int J Obstet Anesth 2019;38:93-103.
3. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg 2015;121:167-71.
4. Gu W, Xu M, Lu H, Huang Q, Wu J. Nebulized dexmedetomidine-lidocaine inhalation as a premedication for flexible bronchoscopy: A randomized trial. J Thorac Dis 2019;11:4663-70.
5. Mason KP, Lerman J. Dexmedetomidine in children: Current knowledge and future applications. Anesth Analg 2011;113:1129-42.
6. Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, *et al*. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg 2002;95:1052-9.
7. Singh AP, Jena SS, Meena RK, Tewari M, Rastogi V. Nebulised fentanyl for postoperative pain relief, a prospective double-blind controlled randomised clinical trial. Indian J Anaesth 2013;57:583-6.
8. Singh J, Premkumar D, Agarwal A. Effect of nebulized versus intravenous fentanyl for postoperative analgesia after unilateral femur interlock surgery. Bali J Anaesthesiol 2020;4:59-61.
9. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. Cephalalgia 2004;24(Suppl 1):9-160.
10. Türkyilmaz EU, Eryilmaz NC, Guzey NA, Moraloglu O. Bilateral greater occipital nerve block for treatment of post-dural puncture headache after caesarean operations. Rev Bras Anestesiol 2016;66:445-50.
11. Bakshi SG, Gehdoo RSP. Incidence and management of post-dural puncture headache following spinal anaesthesia and accidental dural puncture from a non-obstetric hospital: A retrospective analysis. Indian J Anaesth 2018;62:881-6.
12. Mowafy SMS, Ellatif SEA. Effectiveness of nebulized dexmedetomidine for treatment of post-dural puncture headache in parturients undergoing elective cesarean section under spinal anesthesia: A randomized controlled study. J Anesth 2021;35:515-24.
13. Drummond JC, Dao AV, Roth DM, Cheng CR, Atwater BI, Minokadeh A, *et al*. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal human. Anesthesiology 2008;108:225-32.
14. Kumar A, Kumar A, Sinha C, Anant M, Singh JK. Dexmedetomidine nebulization: An answer to post-dural puncture headache? Int J Obstet Anesth 2019;40:155-6.
15. Yoo H, Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, *et al*. Mechanism-based population pharmacokinetic and pharmacodynamic modeling of intravenous and intranasal dexmedetomidine in healthy subjects. Eur J Clin Pharmacol 2015;71:1197-207.
16. Li A, Yuen VM, Goulay-Dufay S, Sheng Y, Standing JF, Kwok PCL, *et al*. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. Br J Anaesth 2018;120:960-8.
17. Abd El-Hamid AM, Elrabeie MA, Afifi EE. Nebulized versus intravenous fentanyl for postoperative analgesia after unilateral arthroscopic anterior cruciate ligament reconstruction surgery: A prospective, randomized, comparative trial. Ain-Shams J Anaesthesiol 2015;8:316-9.
18. Kumari P, Kumar A, Sinha C, Kumar A, Rai DK, Kumar R. Fentanyl vs dexmedetomidine nebulization as adjuvant to lignocaine: A comparative study during awake flexible fiberoptic bronchoscopy. Trends Anaesth Crit Care 2021;37:18-22.
19. Root-Bernstein R, Churchill B, Turke M, Tiruttani Subhramanyam UK, Labahn J. Mutual enhancement of opioid and adrenergic receptors by combinations of opioids and adrenergic ligands is reflected in molecular complementarity of ligands: Drug development possibilities. Int J Mol Sci 2019;20:4137. doi: 10.3390/ijms20174137.
20. Kumar NRR, Jonnavithula N, Padhy S, Sanapala V, Naik VV. Evaluation of nebulised dexmedetomidine in blunting haemodynamic response to intubation: A prospective randomised study. Indian J Anaesth 2020;64:874-9.