Original Research Article

Efficacy of low dose (3µg) dexmedetomidine as adjuvant to 0.5% isobaric ropivacaine in SAB for lower limb surgeries

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Abstract

Background: Dexmedetomidine, a selective α2 adrenergic agonist has found a wide range of applications including intrathecal administration as an adjuvant for local anaesthetics for sub arachnoid block (SAB). **Aim:** To assess the efficacy of low dose 3 µg dexmedetomidine as an adjuvant in SAB with 0.5% isobaric ropivacaine in lower limb surgeries. **Material and methods:** This was a randomised controlled study in which 45 ASA I and II patients, of either sex, aged between 18-60 yrs, with lower limb surgeries requiring sub arachnoid block were assigned to three groups of 15 each. Isobaric ropivacaine 0.5 % was used for this study. The Sub arachnoid block in control group (C) was administered with isobaric ropivacaine 0.5% 3ml and 0.5ml of normal saline, in second group (H) with isobaric ropivacaine 0.5% 3ml and 5 µg dexmedetomidine diluted with 0.5ml normal saline and in third group (L) with isobaric ropivacaine 0.5% 3ml and 3 µg dexmedetomidine diluted with 0.5ml normal saline. The mean times for 2 segment regression, sensory regression to S2 level and rescue analgesia (in mts) in the 3 groups were assessed and compared. Incidence of intraoperative events such as pain, hypotension and sedation amongst the 3 groups was also noted. ANOVA and Fisher's tests were used as appropriate and a $p<0.05$ was considered significant. **Results:** There was a dose dependent significant increase in Mean time for 2 segment regression (61.4±8.30 vs 80.93±12.7 vs 122.93±15.6), regression to S2 (152.93±15.47 vs 239.46±48.38 vs 330.73±34.31) and rescue analgesia (121.13±28.37 vs 179.6±43.03 vs 226.53±35.56) between the plain ropivacaine, 3 µg and 5 µg groups. Incidence of pain was low while that of complications (hypotension and sedation) was significant in the 5 µg group **Conclusion:** Low dose (3 µg) intrathecal dexmeditomidine when used as an adjuvant with plain ropivacaine enhances the duration of postoperative analgesia and provides better quality and duration of sensory block when compared to plain ropivaciane with no additional complications.

Key Word: Dexmedetomidine, Adjuvant, Isobaric Ropivacaine, Sub-arachnoid Block, Lower Limb Surgeries.

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Received Date: 16/08/2018 Revised Date: 12/09/2018 Accepted Date: 14/10/2018
DOI: https://doi.org/10.26611/1015828

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 10 November 2018

INTRODUCTION

Ropivacaine, an amide local anesthetic with a high pKa and low lipid solubility has gained popularity as an intrathecal agent. It may be a suitable alternative as long-acting local anesthetic because it is considered to be less cardiotoxic and has a significantly higher threshold for central nervous system (CNS) toxicity on a milligram basis than bupivacaine [1]. Different concentrations and formulations have been used for intrathecal anaesthesia (0.5% vs 0.75 % [2-4], Isobaric vs Hyperbaric [5-7]). It appears to be less potent and induces less intense motor blockade when compared with bupivacaine (isobaric[8,9] and hyperbaric[10-12]) and the potency dose ratio of bupivacaine: ropivacaine is 1:1.5 as suggested by some studies [9]. It has been reported in some studies that intrathecal injection of isobaric (plain /glucose-free) 0.5% ropivacaine as opposed to isobaric 0.75% ropivocaine of equal volume , a sensory block of very variable extent

How to site this article: Anne Kiran Kumar, Siva Kumar Reddy Lakkireddygari, Sreekanth Yelliboina, Gopinath Ramachandran. Efficacy of low dose (3µg) dexmedetomidine as adjuvant to 0.5% isobaric ropivacaine in SAB for lower limb surgeries. *MedPulse International Journal of Anesthesiology.* November 2018; 8(2): 98-104. http://medpulse.in/Anesthsiology/index.php

because of inadequate distribution and caused intra-operative pain and patient discomfort which had to be managed by supplemental analgesics [2,3] .These studies also suggested that duration of analgesia and motor block were clearly dependant on concentration (absolute dose) of ropivacaine [2-4] . Also, some studies comparing isobaric 0.5% ropivacaine with hyperbaric formulation suggested that plain solutions (isobaric) were less reliable for surgeries above a dermatomal level of L1. So, it seems to be advisable for the consideration of addition of intrathecal adjuvants for 0.5% isobaric ropivacaine for better block characteristics and prolonged post-operative analgesia. Therefore, studies were conducted to elucidate the efficacy of using adjuvants like clonidine[13,14], fentanyl [14] or dexmedetomidine [15]along with isobaric 0.5% ropivacaine , which yielded positive results. Adjuvant drugs added to the intrathecal local anaesthetics can decrease the dose of local anesthetic and provide a better quality of sensory and motor block and also prolong the duration of intraoperative and postoperative analgesia (which is especially useful when lower concentrations or isobaric formulations of ropivacaine are used). Many intrathecal adjuvants like opioids , magnesium, neostigmine , ketamine and midazolam have been used . However addition of opioids to local anaesthetic solution have disadvantages such as pruritus, nausea, vomiting, urinary retention and respiratory depression. Clonidine and dexmedetomidine are α_2-receptor agonists which have sedative (dose-dependent), anxiolytic, analgesic (involving spinal and supraspinal sites), perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing properties without respiratory depression. Intrathecal α_2-receptor agonists are found to have antinociceptive action for both somatic and visceral pain[16]. The affinity of dexmedetomidine to α_2 receptors has been reported to be 10 times more than clonidine[16] and also, Kanazi GE *et al*.,[17] reported a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine. Intrathecal dexmedetomidine has been used (and compared) in different doses (sometimes compared with other adjuvants like clonidine and fentanyl too) along with local anaesthetic solutions of different concentrations and formulations for varied types of surgical procedures. Intrathecal dexmedetomidine has been used in the dose of 3 µg along with 0.5% isobaric ropivacaine[15] or 0.5% hyperbaric bupivacaine[17,18], 5 µg along with 0.5 % isobaric ropivacaine[15] or 0.75% isobaric ropivacaine [19,20] or 0.5% isobaric[21,22] / hyperbaric[23-26] bupivaiane, 4 µg ,6 µg and 8 µg along with 0.5% hyperbaric bupivacaine[27], 10 µg along with 0.75% isobaric ropivacaine[20] or 0.5% isobaric[22]/ hyperbaric[24,28] bupivacaine, 15 µg and 20 µg along with 0.5% hyperbaric bupivacaine[24]. Dexmedetomidine has been used as a supplemental intrathecal adjuvant for many procedures like abdominal hysterectomies[15], transurethral resection of prostate[17,18] and badder tumours[17], gynaecological[21], urological[22], lower abdominal[20,23,24], lower limb orthopaedic[19,25,26], infra umbilical[27] and caesarean[28] surgeries.

MATERIAL AND METHODS

This was a prospective, randomised, comparative study conducted at Nizam's Institute of Medical Sciences, from August to September, 2012.

Inclusion criteria: Patients of age 18 - 60 yrs of either sex, ASA status I and II, undergoing Lower limb surgeries requiring sub arachnoid block (SAB).

Exclusion criteria: Age < 18 or > 60 yrs, ASA status III and IV patients, very long duration surgeries, patients with a history of allergy to either dexmedetomidine or ropivacaine, infection at the puncture site, coagulopathy, history of arrhythmias, and labile hypertension.

General Procedure: 45 patients undergoing lower limb surgeries requiring a SAB were randomly allocated to 3 groups (C, H and L) of 15 patients each. Isobaric ropivacaine 0.5 % was used for this study. Patients in control group (C) had SAB administered with ropivacaine 3ml+ 0.5ml of normal saline. The second group (H) patients were administered ropivacaine 3ml + 5 µg dexmeditomidine diluted with 0.5ml normal saline and the third group (L) patients were administered ropivacaine 3ml+3 µg dexmeditomidine diluted with 0.5ml normal saline. All the routine investigations required for preoperative evaluation and the proposed surgery were done. All the patients were premedicated with tab*let al*prazolam 0.5 mg night before and on morning of surgery. Patients were allowed for a period of absolute fasting of 8 h. In the operation theatre, patients were connected to and monitored with automated noninvasive blood pressure (NIBP), pulse oximetry, and electrocardiogram. Intravenous (IV) access was obtained on the nondominant hand with 18-gauge cannula, All the patients were preloaded with 500 ml of Ringer's lactate before spinal anesthesia. 25G Quincke Babcock spinal needle was introduced through L3–L4 interspace by a midline approach in sitting position using aseptic precautions. Intrathecal injection was given over approximately 15 - 20 s. The control group (C) received isobaric ropivacaine 0.5% 3ml and 0.5ml of normal saline, second group (H) isobaric ropivacaine 0.5% 3ml and 5µg dexmeditomidine diluted with 0.5ml normal saline and the third group (L) isobaric ropivacaine 0.5% 3ml and 3µg dexmeditomidine diluted with 0.5ml normal saline (Dexmedetomidine was drawn in a standard 1 ml insulin syringe ,100 parts = 100 µg and the requisite dose from this syringe diluted with NS). Immediately after

completion of the injection patients were made to lie supine. Oxygen (3 L/min) was administered via a mask. NIBP was measured every 3mts from the point of administering the subarachnoid block for the first 15 mts and every 5 mts thereof till the conclusion of surgery. Hypotension, defined as a decrease of systolic blood pressure by more than 25 % from baseline or a fall below 90 mmHg, was treated with incremental IV doses of mephenteremine 3 mg and IV fluid boluses as required. Bradycardia, defined as heart rate < 50 bpm, was treated with IV atropine 0.3 - 0.6 mg. Sensory testing was assessed by loss of pinprick sensation to 23G hypodermic needle and dermatomal levels were tested every 2 min until the highest level was attained, (usually till T8-T10, the sensory level of which was sufficient for lower limb surgeries) and had stabilized by consecutive tests. Testing was then conducted every 10 min until the point of two segment regression of the block was observed. Further testing was performed at 20-min intervals until the recovery of S2 dermatome. Motor block was assessed by bromage scale every 2 mts till an establishment of a bromage 3 score. On achieving T 8-10 sensory blockade level and a motor block of bromage 3 score, surgery was allowed to commence. The observing anesthesiologist was blinded to the patient group. As our main idea was to to see the efficacy of adding an adjuvant on prolongation of intraoperative and postoperative analgesia , assessment of onset of sensory block , onset and duration of motor block though noted for conduct of the study and progress of the surgery, weren't compared. The adequacy of surgical anesthesia was determined on the basis of the patient's subjective response to surgery and the requirements for supplemental medication to maintain the patient comfortable and pain free. If there was pain or discomfort at the site of surgery, IV Fentanyl 25µg was given. Sedation was assessed with a four point verbal rating scale every 10 mts throughout surgery (1= no sedation, 2= light sedation,3= somnolence, 4= deep sedation) and a score of ≥3 was considered positive for sedation. Postoperatively, the pain score was recorded by using visual analog pain scale (VAS) between 0 and 10 (0 = no pain, 10= most severe pain), every 15 mts for 2 h. Diclofenac 75 mg was given intramuscularly as rescue analgesia when VAS was ≥4. Data regarding the time to 2 segment sensory regression after sub-arachnoid injection of the drug, time to S2 level sensory regression, time to rescue analgesia and the incidence of intra operative pain/patient discomfort warranting supplemental analgesia and other complications like sedation, bradycardia and hypotension were noted

Statistical Analysis: Results were analysed with statistical software SPSS version 20. Mean time for 2 segment regression, sensory regression to S2 level and the mean time for rescue analgesia in all 3 groups were compared. Parametric data were reported as arithmetic mean ± standard deviation and analysed by ANOVA. P< 0.05 considered significant. Fisher's exact test was used for comparing the non parametric data and a p< 0.05 was considered significant.

RESULTS

Table 1: Demographic details in the study (Mean ± SD or Frequencies)

Variables	Ropi +NS Group-C (N=15)	Ropi + 5µg Dexmed Group-H (N=15)	Ropi + 3µg Dexmed Group-L (N=15)	P-Value
Sex- Male/Female	13/2	11/4	12/3	>0.05
Age	33.53 ± 11.66	42.13 ± 12.29	36.80 ± 13.18	>0.05
Weight (kg)	72 ± 1.55	73 ±1.71	73 ± 0.72	>0.05
Height (Cm)	163 ± 1.43	164 ± 1.5	163 ±1.4	>0.05
ASA I/II	12/3	13/2	11/4	>0.05
Duration of surgery (hours)	2.2 ± 1.11	2.18 ± 0.90	1.75 ± 1.1	>0.05

Demographic profile was similar between the 3 groups

Table 2: Comparison of study parameters in the 3 groups

PARAMETER	ROPI +NS GROUP-C	ROPI + 5µG DEXMED GROUP-H	ROPI + 3µG DEXMED GROUP-L	P-VALUE
Mean time for 2 segment regression (min)	61.4 ± 8.30	122.93 ± 15.6	80.93 ± 12.7	0.00
Mean time for regression to S2 (min)	152.93 ± 15.47	330.73 ± 34.3	239.46 ± 48.38	0.00
Mean time for rescue analgesia (min)	121.13 ± 28.37	226.53 ± 35.56	179.6 ± 43.03	0.00

Anova, p< 0.05=s There was statistically significant difference with regards to Mean time for 2 segment regression, Mean time for regression to S2 and Mean time to rescue analgesia with dose dependent prolongation in the 3 µg and 5µg groups when compared with plain ropivocaine group.

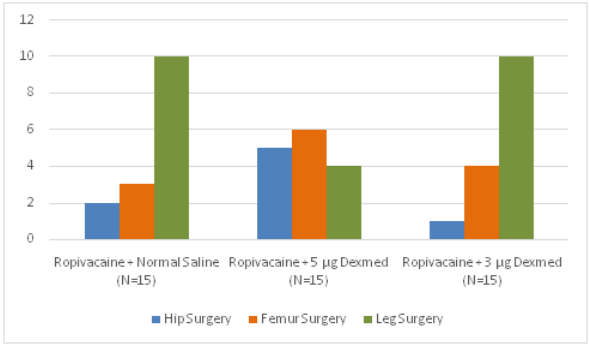

Figure 1: Comparison of Types of Surgeries Between The 3 Groups

Fisher's test, p=0.142 The 3 groups were comparable with regards to the types of surgeries.

Table 3: Comparison of incidence of intra-operative complications in the 3 groups

Complication	Ropi +NS Group-C (N=15)	Ropi + 5µg Dexmed Group-H (N=15)	Ropi + 3µg Dexmed Group-L (N=15)	P-Value
Hypotension	-	4	-	0.031
Pain	3	-	2	0.214
Sedation	-	2	-	0.318

Fisher's test, p <0.05=s There was statistically significant higher incidence of hypotension in the 5 µg group, likewise there was higher incidence of sedation in the 5 µg group though statistically not significant. Though statistically not significant, there was higher incidence of intraoperative patient discomfort and pain in the plain ropivacaine group followed by 3 µg group. There was no bradycardia in any of the 3 groups.

DISCUSSION

Ropivacaine has lower lipid solubility than bupivacaine, which is responsible for its lower penetration into myelinated motor fibers and thus lesser motor blockade with greater sensory- motor differentiation [29]. In view of the reduced toxic potential, ropivacaine has a definite edge over bupivacaine in regional anesthetic techniques requiring large volumes of local anesthetic. However, this drug has also been extensively studied over last many years for its intrathecal use. When identical doses of isobaric ropivacaine and bupivacaine were compared, ropivacaine was found to have almost similar efficacy but shorter duration of sensory and motor block[8]. Incidence of failure is more frequent with intrathecal plain ropivacaine than with plain bupivacaine[30]. Intrathecal injection of plain ropivacaine of lesser concentrations (when equal volumes of different concentrations were compared)[2,3] produced a sensory block of variable extent with considerable number of patients requiring general anaesthesia to accomplish surgery. Failure rates were more with 12 mg[30,31] and 15 mg[7] ropivacaine as opposed to 22.5mg [19] when absolute doses are taken into consideration. Different doses and concentrations of isobaric solutions have been used in varied procedures like lower limb[2,4,8,9,19] caesarian[5,30], perineal[6], lower abdominal surgeries [20] and abdominal hysterectomy[15]. Hyperbaric local anesthetics are known to provide a more predictable spread and higher sensory block.[32]. Hyperbaric preparations of ropivacaine were associated with higher success rate, faster onset, and more consistent and predictable sensory and motor block when compared with isobaric preparations[6,7]. Fettes PD *et al.*, in their study suggested that plain solutions were less reliable for a surgery above a dermatomal level of level L1.When compared to hyperbaric bupivacaine, shorter duration of sensory and motor block and a lesser degree of motor block is produced by hyperbaric ropivacaine[11,12] with significantly lower incidence of hypotension[10]. Ropivacaine is commercially available only as an isobaric preparation and, therefore, hyperbaric solution, if required, needs to be prepared by addition of dextrose. This needs a word of caution as the indigenous mixing of dextrose may present a risk of infection. Hyperbaric ropivacaine has been used for caesarean[5], perineal[6,10], lower limb[7,10,12] and lower abdominal[10] surgeries. Since commercial preparations of hyperbaric ropivacaine are not yet available, adjuvants added to isobaric solution have been considered to overcome the disadvantages of plain ropivacaine (especially lesser concentrations and/or lesser absolute doses) .Adjuvants like clonidine[13,14],

fentanyl[14] and dexmedetomidine[15] have been added to lesser concentrations/doses of isobaric ropivacaine formulations to address it's shortcomings , with positive results . Different doses of dexmedetomidine have been used as adjuvants .When the effect of intrathecal dexmedetomidine using 4 µg , 6 µg, 8 µg on hyperbaric [27] bupivacaine and 5 µg or 10 µg on isobaric ropivacaine [20] or isobaric bupivacaine [22] was investigated, there was dose dependent effect on onset and duration of sensory and motor block [20,22,27], analgesia [20,27] and hypotension [22]. The study by Al-Ghanem SM *et al*., concluded that 5 µg dexmedetomidine seems to be an alternative adjuvant to isobaric bupivacaine, especially in lengthy surgical procedures, with minimal side effects and excellent quality of analgesia. Intrathecal small dose of dexmedetomidine (3 µg) used in combination with hyperbaric bupivacaine in human beings for spinal anaesthesia have been shown to produce a shorter onset of motor block and a prolongation in the duration of motor and sensory block with haemodynamic stability and lack of sedation [17]. In this study we contemplated to use two different (and lesser) doses (3 µg and 5 µg) of dexmedetomidine to 0.5% isobaric ropivacaine to find out the most effective dose, especially with regards to sensory block and analgesic characteristics with least adverse effects. Dexmedetomidine is a new and more selective α_2 receptor agonist compared to clonidine, with higher sedative and analgesic effects. The affinity of dexmedetomidine to α_2 receptors has been reported to be 10 times more than clonidine[16] and also, Kanazi GE *et al*.,[17] reported a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine . Various animal models have documented a dose-dependent synergistic efficacy of α2 agonists added to local anesthetics in spinal anesthesia, with a plateau after a certain dose [33]. Further increase in α2 agonist dose contributes only to increase in the incidence of associated side-effects. De Kock M *et al.,*[34] who used clonidine with ropivacaine intrathecally in three different doses–15,45 and 75 µg for ambulatory knee arthroscopy, observed that small dose clonidine 15 µg significantly improves the quality of anaesthesia without delaying sensory and motor recovery, 45 µg prolongs the sensory blockade without any influence on motor blockade but a dose of 75 µg is associated with delayed sensory and motor recovery as well as detectable side effects as hypotension and sedation , ascertaining a dose dependent effect on spinal block and side effects . So we contemplated, our selected doses of 3 and 5 µg dexmedetomidine to be effective and safe. As depicted in Table-2, there was a dose dependent significant increase in Mean time for 2 segment regression (61.4±8.30 vs 80.93±12.7 vs 122.93±15.6), regression to S2 (152.93±15.47 vs 239.46±48.38 vs 330.73±34.31) and rescue analgesia (121.13±28.37 vs 179.6±43.03 vs 226.53±35.56) between the plain ropivacaine, 3 µg and 5 µg groups as observed in our study. Incidence of pain was low while that of complications (hypotension and sedation) was significant in the 5 µg group as evident from Table -3. Sensory block quality and duration and postoperative analgesia were mainly focused upon and compared in our study rather than onset of sensory or onset and duration of motor block as we wanted to analyse the perioperative analgesic effect of intrathecal dexmedetomidine as an adjuvant to isobaric ropivacaine . The superior quality of sensory block and postoperative analgesia of 5 µg dexmedetomidine as observed in our study is similar to that in other studies too, where it has been used as an adjuvant to isobaric ropivacaine[19,20] or isobaric[21,22] or hyperbaric bupivacaine[23,25,26]. Doses of more than 10 µg[22,24,28] are not advocated for intrathecal use due to the dose dependent bradycardia [24], hypotension [24] or sedation [28] they cause. The incidence of complications (hypotension and sedation) is higher in the 5 µg group in our study. This increased incidence of hypotension[15,22] , sedation[15,23] and bradycardia[19] with 5 µg intrathecal dexmedetomidine has also been seen in other studies wherein it was used as an adjuvant to isobaric ropivacaine[15,19]or isobaric[22] or hyperbaric bupivacaine[23]. The inconsistent sensory block with intraoperative pain and patient discomfort warranting supplemental analgesics (or conversion to GA) observed with plain ropivacaine (especially with lesser concentrations or absolute lower doses) as in our study has been reported by other studies too [2,3,7,15,30,31] .That's the reason why many researchers advocated using a hyperbaric formulation[6,7] or usage of an adjuvant [13,14,15] to circumvent this problem. The better quality of sensory block and postoperative analgesia with no antecedent adverse effects with the 3 µg dexmedetomidine group, as observed in our study are also substantiated by the findings in other such studies wherein it has been used with hyperbaric bupivacaine[17,18]. Though sensory block onset and motor block characteristics not looked into in our study, it would have been much similar to other studies having an enhanced effect with either 3 µg[17,18] or 5 µg [20,21,22,23,25,26] intrathecal dose of dexmedetomidine used along with isobaric ropivacaine[20] or isobaric[21,22] or hyperbaric bupivacaine[17,18,23,25,26]. Dexmedetomidine, owing to its α2 adrenergic agonistic action has an additive or synergistic effect on local anesthetics (due to different mechanisms of action)[35] through prolongation of the sensory block by depressing neurotransmitter release from C-fibers of the spinal cord leading to hyperpolarization of postsynaptic dorsal horn neurons[36]. Motor block prolongation also occurs in conjunction by binding of α2 agonists to motor neuron in

the dorsal horn of spinal cord[37]. Besides this, direct antinociceptive action for control of both somatic and visceral pain further contributes to the prolongation of analgesia duration[16,38]. One of the adverse affects of dexmedetomedine is hypotension as was observed in the 5 µg group in our study.α_2 agonists have shown to decrease intra and post-operative stress response effectively [39]. These agents also have substantial hemodynamic effect in causing hypotension and bradycardia[40]. The incidence of sedation was high, especially in the 5 µg group, in our study. Dexmedetomidine is a partial α_2 agonist. The sedative effects evoked by α_2 agonists are most likely due to the inhibition of pontine locus ceruleus[41], which is densely populated with α_2 adrenoceptors and is an important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance. Kang SH *et al*.,[42] reported that dexmedetomidine administration during surgery reduced intraoperative and post-operative secretion of cytokines, including the pro-inflammatory cytokines tumour necrosis factor-α, interleukin-1β and IL-6 and anti-inflammatory cytokines IL-4 and CRP level in their study. Dexmedetomidine can be considered as an intrathecal adjuvant for surgeries due to these other beneficial systemic effects. In summary, the use of low dose of dexmedetomidine (3µg) as an adjuvant to isobaric ropivacaine in spinal anaesthesia provides better intraoperative somato-visceral block characteristcs and postoperative analgesia without significant incidence of side effects.

CONCLUSION

Adjuvant effect of low dose (3µg) intrathecal dexmeditomidine is beneficial when added to plain ropivaciane, with prolonged duration of analgesia and better sensory block characteristics, without much of it's antecedent adverse effects. Overall duration of analgesia was less when compared to 5 µg dexmeditomidine, but with decreased complications (in terms of hypotension and sedation).

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Source of Support: None Declared
Conflict of Interest: None Declared