

Comparison of Dexmedetomidine V/S Propofol Used As Adjuvant with Combined Spinal Epidural Anaesthesia for Joint Replacement Surgeries

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Abstract: The increased use of regional anaesthesia in recent years has led to an increased need for sedation during surgery in awake patients. Our study aim to compare the hemodynamic, duration of anaesthesia and perioperative adverse events with intravenous Dexmedetomidine and intravenous Propofol when used as an adjuvant to regional anaesthesia in joint replacement surgeries. Prospective pilot study enrolled 100 patient posted for unilateral knee replacement surgery, divided in two groups— Dexmedetomidine – group D and Propofol – group P. Patient in Group D receive intravenously Dexmedetomidine which is diluted with normal saline in a concentration of 4µg/ml and Group P receive intravenously Propofol in a concentration of 10mg/ml, firstly a loading dose and then a maintenance infusion titrated to achieve OAA/S score of 3, as per study protocol. Analysis of significance of study parameters on continuous scale by student T test, (intergroup analysis) in means between two groups and the difference in proportion by using chi square test. Significance is assessed at 5% level of significance. P value < 0.05 was considered significant. Patients in Group – D resulted to have lower heart rate in both intraoperative and postoperative periods, lower value for postoperative blood pressure, lower postoperative respiratory rate and lower postoperative OAA/S score with significant p value < 0.05. Patients in Group – P resulted to have lower intraoperative value for blood pressure, respiratory rate and OAA/S score. Additionally Dexmedetomidine resulted in better preservation of patient arousability, prolongs the effect of neuraxial blockade and have lower incidence of untoward side effect like hypotension and bradycardia. Low dose infusions of Dexmedetomidine provides an added advantage of having lesser untoward side effects and longer duration of motor block, which is desirable in joint replacement surgeries under regional anaesthesia.

Keywords: Dexmedetomidine, Propofol, Total knee Replacement Surgery, Spinal - Epidural anaesthesia.

INTRODUCTION

Adjuvants are pharmacological or immunological agent which is used to modify the effects of the drug to produce a desired result. The increased use of regional anaesthesia in recent years has led to an increased need for sedation during surgery in awake patients. Sedation is known to increase patient's acceptance of regional anaesthesia and to greatly improve patient wellbeing during the surgical procedure. Many agents (Midazolam, Ketamine, Remifentanyl, Propofol and Dexmedetomidine, etc) have been used for this purpose [1].

Sedation and analgesia includes a continuum of states of consciousness ranging from minimal sedation (anxiolysis) to general anaesthesia. Vigilant monitoring is required because patients may rapidly progress from a "light" level of sedation to "deep" sedation and

ultimately, unconsciousness [2]. As a result, patients may be at risk for airway obstruction, oxygen desaturation and even aspiration.

The ideal sedative medication for use during surgery would provide:

- Easily titratable level of sedation
- Decreased anxiety
- Predictable amnesia
- Provide for a rapid recovery with minimal side effects

Propofol is commonly used in subhypnotic dosages for conscious sedation in combination with local anaesthesia, mainly because it is a short acting, easily controllable and individually titratable hypnotic and sedative agent [3].

Dexmedetomidine is a α -2 agonist that has been used for pre-medication and as an adjunct to general anaesthesia[4] and regional anaesthesia and provides sufficient sedation and had few side effects. The anesthetic and the analgesic requirement get reduced to a huge extent by the use of Dexmedetomidine because of their analgesic properties and augmentation of local anesthetic effects [5].

Objectives

Primary: To compare the effect of intravenous Dexmedetomidine (Group D) with intravenous Propofol (Group P) on hemodynamics (Heart rate, Blood pressure), Respiratory rate and Peripheral Oxygen saturation when used as an adjuvant to Regional anaesthesia in patients undergoing unilateral knee joint replacement surgery.

Secondary: To compare the effect of intravenous Dexmedetomidine (Group D) with intravenous Propofol (Group P) on Sedative effect, Duration of regional anaesthesia and Peri-operative adverse events when used as an adjuvant to Regional anaesthesia in patients undergoing unilateral knee joint replacement surgery.

MATERIALS AND METHODS

Prospective pilot study is conducted in the multi-specialty surgical operation theatre and post anaesthesia care unit. The Sample size was calculated at power 80% and alpha error 0.05 assuming SD of 3 min. In time to achieve mean sedation score and 10% difference in the intraoperative mean blood pressure and heart rate. It is further enhanced and rounded off to 50 cases equally divided into each groups. After obtaining the approval of the ethics committee of the Hospital and an informed consent given by each patient, 100 ASA grade I or II patient, aged 40- 70 years, who are posted for unilateral knee replacement surgery are enrolled in the study over a period of 18 months. Patients are divided in two groups – Dexmedetomidine – group D and Propofol – group P on 1:1 basis. Criteria of exclusion for the study given in table 1.

Preanaesthetic evaluation including history, clinical examination, systemic examination of cardiovascular, respiratory, central nervous system was carried out. Examination of spine for deformity, infection and airway examination was done. The patients were advised overnight fasting over 8 hours.

On receiving in operative room, all the patients are hydrated with 10 ml/kg of normal saline solution via an 20-gauge IV cannula before combined spinal epidural anaesthesia. With the patient in the sitting position, a combined spinal epidural block is performed at the level of L3 - L4 through a midline approach. After 10 mins of performing CSEA, conforming the fixation of block, and, having mean blood pressure above 60 mmHg, infusion of experimental drug is started.

Patient in Group D then started to receive intravenously Dexmedetomidine which is diluted with normal saline in a concentration of 4 μ g/ml with loading dose of 0.50 μ g/kg Dexmedetomidine over 10 minutes and then a maintenance infusion titrated to achieve the OAA/S score of 3, starting with the dose of 0.5 μ g/kg/hr. The patients who are allocated to Group P receive intravenously Propofol in a concentration of 10mg/ml with loading dose of 1mg/kg bolus over 10 min and then a maintenance infusion titrated to achieve OAA/S score of 3, starting with the dose of 1 mg/kg/hr.

Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean blood pressure, Oxygen Saturation, Respiratory rate, Modified Bromage score (table 2) and Modified Observer's Assessment of Alertness/Sedation scale (Table 3) are recorded intraoperatively till the surgery lasts (max 120 mins) and then in PACU till the Bromage scale return to zero. Perioperative adverse events like heart rate less than 60/min, bradycardia (heart rate less than 50 /min), hypotension (MAP less than 60 mmhg), respiratory depression (SPO₂ less than 90%) and perioperative nausea and vomiting are also noted.

Data collection and analysis

A study proforma was formulated and details of demographic characteristics, baseline vitals and investigations, intraoperative and postoperative variables were recorded for all the patients in the study. The qualitative data are presented as proportion and percentage and the quantitative data are presented as mean and standard deviation. Student's t test is used to find out the significance of study parameters on continuous scale, (intergroup analysis) in means between two groups are analyzed by and the difference in proportion is analyzed by using chi square test. Significance is assessed at 5% level of significance. P value < 0.05 was considered significant.

RESULTS

Total of 100, ASA grade I-II patients were enrolled in the study over a period of 18 months. All the demographic characteristics, Age, Sex, weight and height were comparable in both the groups (p value >0.05). Preoperative co-morbidities (Hypertension, Diabetes Mellitus, Hypothyroidism, COPD, CAD), preoperative investigations (Hemoglobin, TLC, Platelet count, S. Creatinine, S. Sodium, S. Potassium and Left Ventricular ejection Fraction) as well as preoperative hemodynamic variables, respiratory rate and peripheral oxygen saturation among both the groups were compared and no significant difference is observed among both the groups(p value >0.05). Mean duration of surgery which was taken as time from initiation of neuraxial block to surgical closure is comparable in both the groups (101.88 \pm 9.997 min for group D and 102.54 \pm 10.408 min for group P with P value > 0.05 and so the mean duration of sedative infusion is also similar in both the groups.

The mean Heart rate during intraoperative period, when compared in both the groups, the difference remained insignificant for the initial 10 min, although it decreases from baseline under the effect of neuraxial block. However after the initiation of drug infusion, the mean heart rate further decreases and after 10 min of infusion, the difference became significant with mean heart rate higher in Propofol Group (Group P- 65.64±5.38 bpm v/s Group D- 59.62±6.18 bpm). The difference remains significant throughout the infusion time and increases as the duration of surgery progresses with P value < 0.05. (Table 4).

The initial fall in mean systolic and diastolic blood pressure seen in first 10 minutes is under the effect of neuraxial block. Subsequently more pronounced fall is seen in Group P, the difference being significant after 15 mins of duration (5 mins after starting the drug infusion). Mean difference in systolic BP between both the groups ranging from 6.9 to 15.5mmhg in first hour, which progressively increases as duration increases, but as the drug infusion is stopped at the end of surgery, the hypotensive effect of Propofol diminishes faster decreasing the mean difference among the groups. The mean blood pressure was significantly lower in group P after 15min, difference progressive increase during intraoperative period. Significantly lower mean respiratory rate is observed intraoperatively in group P as compared to group D after 30 mins, further decreasing upto 45 mins and then showed progressive increment. No significant difference is observed in mean peripheral oxygen saturation among both the groups intraoperatively.

Modified Bromage score became fixed to Bromage 3 after fixation of neuraxial block among both the groups. During Intraoperative period, no significant difference is observed to achieve Bromage score 3 among both the groups.

Although sedation is maintained in conscious sedation range, mean OAA/s score remain significantly

lower in Group P. The difference is high at the start of infusion of drugs as patients in Group P achieve lower score earlier. Again the difference is high at the end of surgery, as the sedative effect of Propofol reduces faster than Dexmedetomidine, resulting in Lower OAA/s score in Group D. Significantly higher time to achieve desired sedation is required in group D (mean 16.50 ± 2.24 mins) as compared to group P (mean 6.82 ± 1.62 mins) (Table 5).

The mean postoperative heart rate was significantly higher in group P, the difference increases for the initial 30 - 45 mins of post-operative period, mean difference reached its peak (17.46 bpm) at 30 mins post op. Significantly higher mean blood pressure is observed in group P as compared to group D during post-operative period (table 6).

Postoperatively mean Bromage scale score remain significantly higher in group D as compared to group P. Duration of regression of Bromage score to 0 is observed significantly higher in group D (215.08 ± 15.45 mins) as compared to group P (180.24 ± 12.80 mins). Post operatively the mean OAA/S score remain significantly lower in group D in comparison to group P.

On comparing heart rate among both the groups, 70% of patients in group D have HR < 60 whereas 24% patients in group P have HR < 60. Bradycardia defined as HR < 50 in our study is seen in 10% patients in group D whereas only 2% patients in Group P. Hypotension defined as mean blood pressure < 60 in our study is seen in only 2% patients in Group D whereas 20% patients in group P experienced hypotension. None of the patient in either group experienced respiratory depression defined as peripheral oxygen saturation < 90%. Perioperative Nausea and Vomiting is seen in 5% patients in group D whereas 8% patients in Group P.

Table-1: Criteria of exclusion

- Patient who is not able to provide legal consent for the procedure.
- Patient receiving an experimental drug like Dexmedetomidine or other α_2 agonists, within 28 days before surgery
- Second or third degree heart block
- Abnormal renal function tests
- Patients having current history of psychiatric disorder
- Presently on psychotropic medications
- Ejection fraction < 50%
- History of sleep apnea
- Body weight more than 50% higher than ideal body weight.
- Height less than 150 cm

Table-2: The modified Bromage scale

Bromage 0	-	the patient able to move the hip, knee and ankle;
Bromage 1	-	the patient is unable to move the hip, but is able to move the knee and ankle;
Bromage 2	-	the patient is unable to move the hip and knee, but is able to move the ankle;
Bromage 3	-	the patient is unable to move the hip, knee and ankle

Table-3: Modified Observer’s Assessment of Alertness/Sedation Scale

Responsiveness	Score
Agitated or Anxious	6
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

Table-4: Comparison of intraoperative Change in Heart rate per minute among the groups

		Heart rate per minute (mean ± SD)										
Duration(min.)		0	5	10	15	30	45	60	75	90	105	120
Group D	N	50	50	50	50	50	50	50	50	50	42	17
	Mean	77.36	73.82	70.38	64.54	59.62	57.52	57.22	57.10	57.20	57.76	60.94
	SD	6.66	7.12	6.63	7.13	6.18	7.09	5.17	4.73	5.11	4.99	5.49
Group P	N	50	50	50	50	50	50	50	50	50	37	10
	Mean	75.84	72.64	68.20	63.92	65.64	66.86	66.92	67.66	68.68	70.97	72.30
	SD	5.02	6.39	5.71	6.06	5.38	5.77	4.99	4.57	3.95	3.69	3.06
P Value		0.20	0.39	0.08	0.64	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Difference		1.52	1.18	2.18	0.62	-6.02	-9.34	-9.70	-10.56	-11.48	-13.21	-11.36
LS		NS	NS	NS	NS	S	S	S	S	S	S	S

Table-5: Comparison of the mean intraoperative OAA/S score among the groups

		INTRAOPERATIVE OAA/S SCORE										
Duration (min.)		0	5	10	15	30	45	60	75	90	105	120
Group D	N	50	50	50	50	50	50	50	50	50	42	16
	Mean	5.28	5.26	5.00	4.46	3.08	3.00	3.00	3.00	3.00	3.00	3.00
	SD	.454	.443	0.000	.503	.274	0.000	0.000	0.00	0.00	0.00	0.00
Group P	N	50	50	50	50	50	50	50	50	50	35	12
	Mean	5.4	5.20	5.00	3.64	3.00	2.82	2.88	2.92	2.98	3.17	3.75
	SD	.495	.404	0.000	.485	0.000	.388	.328	.274	.141	.382	.452
Mean Difference			-0.12	0.06	0.00	0.82	0.08	0.18	0.12	0.08	0.02	-0.17
P Value			0.21	0.48	NA	<0.001	0.42	<0.01	0.01	0.04	0.32	0.01
LS			NS	NS	NA	S	NS	S	S	S	NS	S

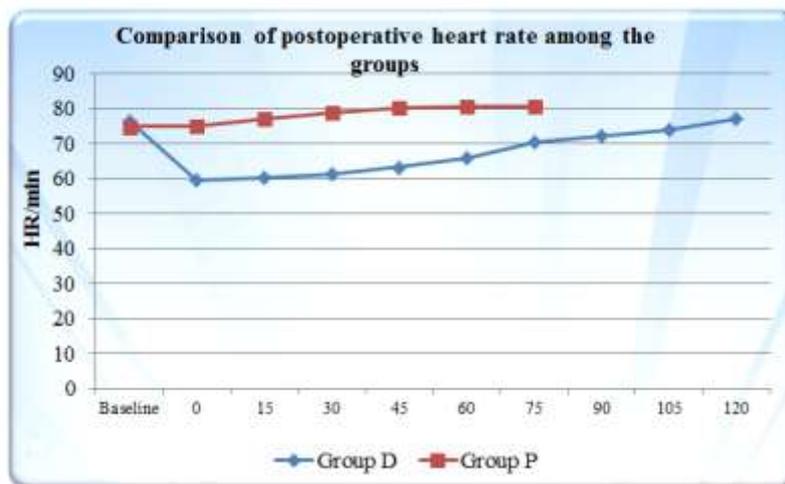


Fig-1: Comparison of postoperative changes in heart rate among the groups

DISCUSSION

Central Neuraxial and Regional anaesthesia are time honoured procedures for producing surgical analgesia and it offers certain advantages over general anaesthesia. In order to improve patient acceptability and comfort and to reduce stress it is necessary to provide some form of sedation during the operation.

Propofol is a short acting intravenously administered hypnotic agent. It is used for induction and maintenance of general anaesthesia, sedation of mechanically ventilated patients, procedural sedation and as an adjuvant to Regional anaesthesia (neuraxial blocks and peripheral nerve blocks) [6]. The effect on Gabaergic receptor activity and also recently suggested activity through endocannabinoid system contribute to the anesthetic action and unique properties of Propofol. The rapid onset and recovery characteristics along with amnesic effects have lead to widespread use of Propofol.

Dexmedetomidine is selective α_2 -agonist and produces sedation and anxiolysis by binding to α_2 -receptors in the locus coeruleus, which diminishes the release of norepinephrine and inhibits sympathetic activity, thus decreasing heart rate and blood pressure [7]. It produces analgesia by binding to adrenoreceptors in the spinal cord. Activation of presynaptic α_2 -A receptors at locus coeruleus decreases norepinephrine release and causes sedative and hypnotic effects, whereas its effect on descending medullo-spinal noradrenergic pathway results in analgesia by terminating pain signal propagation. At substantia gelatinosa of the spinal cord, it decreases firing in nociceptive neurons and release of substance P, thus producing analgesia. So, Dexmedetomidine has a role in modulating pain and inhibiting the transmission and perception of pain. Activation of post-synaptic α_2 -A receptors in CNS results in hypotension and bradycardia by decreasing the sympathetic activity. Activation of post-synaptic α_2 -C

receptors in CNS results in anxiolysis, whereas activation of post-synaptic α_2 -B receptors in peripheral vasculature results in transient hypertension[8].

Our study showed that after the initiation of drug infusion, the mean heart rate decreases and after 10 min of infusion, the difference became significant with mean heart rate higher in Propofol Group. The difference remains significant throughout the infusion time and increases as the duration of surgery progresses. *Abdelkarim S. et al.*[9] study showed similar results with decrease in heart rate with the start of infusion and the decrease is more clear and significant with Dexmedetomidine. Similar results are seen in the study done by *Yusuke kasuya, et al.*[10] and *Arian and Ebert et al.* [11], which showed significant decrease in heart rate with Dexmedetomidine.

In contrast to our result *Nadia MN et al.*[12] and *Ashraf Ghali, et al.* [13], although noticed fall in mean heart rate from baseline in both the groups but when compared both groups had similar reduction from baseline. Our study showed significant reduction in blood pressure within 5 mins of start of Propofol infusion and then it remains significantly low in comparison to Dexmedetomidine group. In Dexmedetomidine group, the significant fall in systolic blood pressure is seen after 10 min of drug infusion and it again increases slightly and remains so through the drug infusion period. The effect is more pronounced on systolic blood pressure in both the groups whereas Propofol infusion also leads to highly significant fall in diastolic blood pressure for 5 - 10 min of start of infusion (loading dose). The mean blood pressure remain significantly low with Propofol intraoperatively after 30 min (p value < 0.05) but it became less significant or eventually non-significant towards the end of surgery as the infusion's rate is decreased or stopped.

Study done by *Arian and Ebert et al.*[11] showed similar results with MAP being less in

Propofol group (average 11 mm when compared with the Dexmedetomidine group but postoperatively MAP is lower in Dexmedetomidine group at an average of 8 mm Hg).

The effect of Propofol infusion on HR and MAP is due to powerful inhibitory effect of Propofol on sympathetic outflow. Dexmedetomidine is also known to decrease central sympathetic outflow and circulating catecholamine levels and would therefore be expected to cause decrease of MAP. However large doses of Dexmedetomidine have a direct effect at the post synaptic vascular smooth muscles to cause vasoconstriction and it is possible that the sympathoinhibitory effect is slightly opposed by direct α_2 – mediated vasoconstriction. In contrast, Propofol has no direct activity on vascular smooth muscles. The decrease in the HR might be attributed to the sympatholytic effects and in part because of a vagal mimetic effect of Dexmedetomidine.

In PACU, the patients in group D have significantly less heart rate and blood pressure values than the patients in group P. This is in contrast to the intraoperative values of blood pressure where group P have less blood pressure values. Similar postoperative results were described by *Arain and Ebert et al.* [11]. This could be due to the persistent effect of Dexmedetomidine in PACU, as the elimination half-life of Dexmedetomidine has been described as around 2 hours compared to elimination half-life of Propofol of around 20 - 60. Again persistent plasma levels of Dexmedetomidine in PACU could still maintain the sympatholysis, but perhaps they are too small to cause significant postsynaptic direct α_2 – mediated vasoconstriction.

The mean respiratory rate remain similar for the first 10, but after the start of infusion, the respiratory rate is less in group P as compared to group D. The difference became highly significant after 5 of infusion of the drug with the P value \ll 0.05.

Abdelkarim S. et al. [9] compared the effect of Dexmedetomidine and Propofol on arterial CO₂ and found that although there was increase in arterial CO₂ level, it was not clinically significant as the readings were under normal range. The difference in the results could be due to the differences in the regimen of drug infusions or the combination of narcotics.

The time to achieve the desired sedation is significantly high in Dexmedetomidine group D. The result can be attributed to the short onset of action of Propofol. *Arain and Ebert et al.* [11] also studied the onset time and found similar results that Dexmedetomidine infusion group patients needed more time in comparison to Propofol group Patients to achieve target sedation level. Also they concluded that persistent effect of Dexmedetomidine in recovery room,

resulted in significantly more sedation when compared to short acting Propofol. However, patients were easily aroused to perform the psychomotor testing and their performance was not importantly impaired compared with the Propofol. This is consistent with one of the interesting characteristics of Dexmedetomidine, which is the ability to achieve sedation but preserves patient arousability.

The time required to regress to Bromage score 0 is significantly prolonged in Dexmedetomidine group. α_2 –adrenergic receptor agonists such as Clonidine and Dexmedetomidine when used intrathecally with local anesthetics can strengthen the effect of the local anesthetic. The amount of local anesthetic needed are reduced and the time of sensory blockade and motor blockade is extended. Although usefulness and stability of Dexmedetomidine are confirmed but *Konacki et al.* [14] in their study found Dexmedetomidine to have harmful effect on Myelin sheath when administered intrathecally or epidurally. Dexmedetomidine gives direct anesthetic effect by affecting brain and spinal neural tube. It also acts as a vasoconstrictor, decreases the amount of inhalation anesthetics and narcotic analgesics which are needed during general anaesthesia. It also interacts with local anesthetics, decreases the needed amount and increases the effect. Also it is known to increase the sensory blockade of anaesthesia and extends the analgesia request time for patients for the first time after the surgery.

Comparing the adverse events in our study, Group D had significant incidences of Bradycardia (70%), contrast to *Abdelkarim et al.* [9] showed lower heart rate in Dexmedetomidine group but no significant bradycardia seen in any patient. *Hong Jy, Kim woo et al.* [15] and *Elcicek K, Tekin M et al.* [16] showed prominent bradycardia effect with incidence ranging from 30%- 40%, whereas study done by *SS Harsoor et al.* [17] showed no significant bradycardia.

Ashraf Ghali, Abdul Kader Mahfouz, et al. [18] reported no event of bradycardia, hypotension, desaturation, nausea and vomiting or dry mouth in any of the group, when they compared Dexmedetomidine and Propofol as a sedative for vitreoretinal surgery.

Study by *Arain and Ebert et al.* [11], *Ashraf Ghali et al.* [18] and *Nadia MN et al.* [12] also shown better result with Dexmedetomidine in terms of surgeon's satisfaction, overall patient's satisfaction, analgesic sparing effect and better control of postoperative shivering.

There are limitations in our study. First, there is no control group as it would be unethical to deprive patients to any form of sedation. Second, hemodynamic parameters are recorded at a particular interval, within which significant changes may have occurred and missed. Third, the study is done in controlled conditions

in healthy patients; results may differ in patients with uncontrolled co-morbidities and in critical care settings. Fourth, Plasma drug concentration may differ even after similar dose regimens which may resulted in difference in results.

CONCLUSION

The supplementation of intravenous Dexmedetomidine and Propofol as an adjuvant to regional anaesthesia at appropriate infusion rates produce good level of sedation in all the patients and alleviates the fear and anxiety of patients. Both the drugs resulted in decrease in heart rate and mean blood pressure which is helpful in minimizing surgical site bleeding. Neither Dexmedetomidine nor Propofol resulted in respiratory depression. Additionally Dexmedetomidine resulted in better preservation of patient arousability and also prolongs the effect of neuraxial blockade. Also lower dose of Dexmedetomidine has an added advantage of lower incidence of untoward side effect like hypotension and bradycardia.

Our study suggest that both Propofol and Dexmedetomidine are indeed useful adjuvant to regional anaesthesia with good hemodynamic and respiratory parameters preservation, but low dose infusions of Dexmedetomidine provides an added advantage of having lesser untoward side effects and longer duration of motor block, which is desirable in knee and hip replacement surgeries under regional anaesthesia.

KEY MESSAGE

Both Propofol and Dexmedetomidine are indeed useful adjuvant to regional anaesthesia with good hemodynamic and respiratory parameters preservation, but low dose infusions of Dexmedetomidine provides an added advantage of having lesser untoward side effects and longer duration of motor block, which is desirable in knee and hip replacement surgeries under regional anaesthesia.

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