Original article:

Comparative study of postoperative analgesia in dexmedetomidine versus magnesium sulfate pretreated patients undergoing elective infraumbilical surgery under subarachnoid block

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Abstract:

Backgrounds: Dexmedetomidine being a α_2 agonist provides excellent sedation with minimal respiratory depression, decreases postoperative requirement of analgesics and may also acts as an adjuvant in subarachnoid block (SAB). Intravenous infusion of magnesium sulfate during SAB has also been used to improve postoperative analgesia and to reduce the total consumption of analgesics.

Material and Methods: Seventy four American Society of Anaesthesiologist grade I-II patients, aged 18-65 years old of either sex, scheduled for infraumbilical surgery under SAB were randomly allocated into group-D (dexmedetomidine 1µ gm/kg) and group-M (magnesium sulfate 50 mg/kg). Anaesthesia techniques were standardized. The highest sensory block level, the recovery time of both sensory and motor block, intraoperative Ramsay sedation score (RSS) and postoperative visual analogue scale (VAS) score, time of rescue analgesia and total postoperative requirement of diclofenac were compared.

Results: Maximum upper level of sensory block following SAB was higher in group-D (*p* value < 0.001). Time of regression of sensory and motor block, time of rescue analgesia was longer in group-D (*p* value < 0.001). Depth of sedation was higher in group-D though oxygen saturation and respiratory rate was comparable in both groups. Postoperative VAS score and total requirement of diclofenac (*p* value < 0.001) was lower in dexmedetomidine group.

Conclusion: Single dose intravenous dexmedetomidine before subarachnoid block is more efficacious than single dose intravenous magnesium sulfate to provide postoperative analgesia as evident by reduce analgesic requirements.

Key words: Subarachnoid block, dexmedetomidine, magnesium sulfate, infraumbilical surgery.

INTRODUCTION

Spinal anesthesia (SAB) was first described by August Bier in 1898, using 3ml of 0.5% cocaine[1]. The technique has been refined since that time and has been evolved into the modern concept of intrathecal, spinal or subarachnoid block (SAB). Regional anesthesia offers several advantages over general anesthesia for infraumbilical surgery like decrease incidence of deep vein thrombosis (DVT) and amount of operative blood loss[2]. Among regional anesthesia, spinal anesthesia is a frequently used technique in infraumbilical surgery.

Patients undergoing infraumbilical surgery under spinal anesthesia with hyperbaric bupivacaine alone occasionally experienced varying degree of intraoperative pain and discomfort in spite of apparently adequate level of sensory block. Moreover management of postoperative pain and its complication still continue to be a challenge in postoperative care. There is a continuous search for newer agents and methods to reduce adverse effects of systemically administered analgesic.

Different adjuvants[3] have been used to prolong subarachnoid block, to delay onset of postoperative pain and to reduce analgesic requirements. Use of opioids as adjuvant have some adverse effects like nausea and vomiting, urinary retention, constipation and depression of ventilation [4]. So other adjuvants like tramadol , a partial opioid agonist (weak μ agonist)[5] and midazolam[6], a benzodiazepine were also tried in this respect but these are not devoid of adverse effects. Many clinical studies have been carried out using intrathecal alpha-2 agonist like clonidine and dexmedetomidine as adjuvants to local anesthetics [7,8,9].

The role of magnesium for perioperative analgesia has been investigated in several studies and it has been reported to be effective in perioperative pain treatment and in blunting somatic, autonomic and endocrine reflexes provoked by noxious stimuli[10,11,12,13,14]. The usefulness of magnesium for postoperative analgesia is not only limited to general anesthesia but also in spinal anesthesia when administered via both intravenous[15,16] or intratheca route[17].

Magnesium can prevent the induction of central sensitization from peripheral nociceptive stimuli at the spinal action site by blocking NMDA receptors in a voltage dependent manner[18]. Intravenous infusion of magnesium sulfate during spinal anesthesia was reported to improve postoperative analgesia and to reduce the total consumption of analgesics[15].

Dexmedetomidine, an alpha 2 agonist having sedative, analgesic, and anesthetic sparing effect, has also been used for premedication in general anesthesia[19].It has also been used safely as premedicant or as a sedative in patients undergoing surgical procedures under regional anesthesia[20,21,22] . There are very few data regarding the effect of single dose[23] intravenous dexmedetomidine before subarachnoid block on duration of spinal analgesia and total postoperative analgesics consumption.

MATERIALS AND METHODS

After availing proper approval from institutional Ethics committee, this randomized controlled parallel-group single blind clinical trial was carried out on 74 patients, admitted in IPGME&R and SSKM Hospital, Kolkata, for undergoing infraumbilical surgery. Patients aged > 65 and <18years, of higher American Society of Anesthesiologist (ASA) grade (ASA> II), unable to give written consent, carrying pregnancy and having any other contraindication for administration of (SAB) (i.e infection at the site of injection, coagulopathy, neurological disorder, hemodynamically compromised patients, known allergy to bupivacaine/dexmedetomidine/ magnesium sulfate ,patients on anticoagulants or on antiplatelet drugs), known allergy to dexmedetomidine and magnesium sulphate were excluded from this study. Following performing complete pre-anesthetic evaluations, written informed consent was obtained and all patients were kept on fasting at least for 8 hours. After receiving them in operation theatre, an intravenous line was established with 18G IV cannula in a large peripheral vein and 500ml of 0.9% of normal saline was infused. All patients were attached to the monitors as per standard ASA monitoring and randomly allocated into two equal groups. Group-D received intravenous dexmedetomidine 1mcg/kg in 100 ml normal saline over 15 minutes and group-M received magnesium sulfate 50 mg/kg in the same

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manner. Five min following the end of the infusion, dural puncture was performed at the L3-L4 interspace using a standard midline approach in lateral decubitus position with a 25G Quincke's needle. Bupivacaine (heavy) 0.5%, 3ml was injected intrathecally. All patients received moist oxygen via bi-nasal cannulae throughout the procedure.

Level of sensory blockade was checked after 5 minutes with an alcohol swab in mid axillary line. Recovery time for sensory blockade was defined as two dermatome regression of anesthesia from maximum level.

Motor blockade was assessed immediately after sensory block assessment using a Modified Bromage scale (Modified Bromage 0, the patient is able to move the hip, knee and ankle; Modified Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle; Modified Bromage 2, the patient is unable to move the hip and knee, but is able to move the ankle; Modified Bromage 3, the patient is unable to move the hip, knee and ankle). Motor block duration time was the time for return to Modified Bromage Scale1.

The highest sensory block level and recovery time of both sensory and motor block were recorded.

The level of sedation was evaluated both intraoperative and postoperatively using Ramsay Sedation Scale [RSS]: (1.Patient anxious, agitated, or restless; 2. Patient cooperative, oriented, and tranquil alert; 3. Patient responds to commands; 4. Asleep, but with brisk response to light glabellar tap or loud auditory stimulus; 5.Asleep, sluggish response to light glabellar tap or loud auditory stimulus.6. Asleep, no response). Excessive sedation was defined as score greater than 4/6.

Hypotension (defined by a decrease in mean arterial blood pressure [MAP] below 20% of baseline or systolic blood pressure [SBP] <100 mm Hg) [24] was treated with 200ml of bolus Ringer`s solution intravenously if not corrected then mephentermine (6 mg). Bradycardia (heart rate <50 beats/ min) was treated with intravenous atropine (0.6 mg). Any adverse reaction was noted and treated accordingly.

At the end of the procedure patients were sent to the postoperative room. Postoperative analgesia were assessed by visual analogue scale [VAS] pain score (VAS 0 = no pain, 100 = worst possible pain) at 4, 8, 12 and 24 postoperative hours. . Rescue analgesia in the form of injection diclofenac 75mg intramuscular was administered when VAS score > 40 or on demand.

Duration of postoperative analgesia, time of requirement of 1st rescue analgesic, total requirement of diclofenac in first 24 hours postoperative period were recorded and compared. Adverse reactions like episodes of hypotension, bradycardia, desaturation, respiratory depression, perioperative sedation score, VAS score, perioperative total requirement of mephentermine and atropine were also noted.

Data were summarized by mean and standard deviation for numerical variables and counts and percentage for categorical variables. Numerical variables were compared between groups by student`s unpaired t test if normally distributed or by Mann-Whitney U test if otherwise. The chi square test or Fisher`s exact test was employed for comparing independent proportions. All analysis was two tailed and $p < 0.05$ was taken as statistically significant.

RESULTS AND ANALYSIS

Demographic data between the groups were found to be statistically insignificant (p value > 0.05)[Table : 1]

Following 5 minutes of administration of subarachnoid blocks maximum upper level of sensory blocks were found significantly higher in group-D (*p* value < 0.001) and the mean of two segment(dermatome) regression time of sensory blocks in dexmedetomidine group was 178.00±8.446 minutes which was much longer than group-M (160±8.206 min)[*p* value <0.001]. Even, regression of motor blockade to Bromage 1 took longer time in group-D (201.78±9.875 min) compared with group-M (176.35±7.962 min) [*p* <0.001]. First request for attenuating postoperative pain from the patients treated with dexmedetomidine were delayed (p value <0.001) and total doses of diclofenac requirement in postoperative 24 hours were significantly less in group-D (p value < 0.001). [Table: 2]

Comparison of perioperative haemodynamic stability of these two groups were done by measuring heart rate (HR), SBP, diastolic blood pressure (DBP) and MAP at different time intervals from instillation of SAB to 24 hours postoperative period. It was evident that there was no significant difference in SBP, DBP, MAP at baseline but then there was a significant decrease of SBP, DBP, MAP was noted in dexmedetomidine group from 5 minutes to 80 minutes of intraoperative period. [Table: 3] Hypotensive episodes were treated with mephentermine but the total dose requirement of it was comparable in both groups (*p* value 0.474).[figure: 1] Though SBP was comparable in this two groups at postoperative period up to 24 hrs, MAP and DBP were definitely lower around 12th hour of postoperative period. MAP was found to be comparable around 24th hour but DBP remained lower in group-D though it did not produce any discomfort to the patients. No significant changes of heart rate were found at any timeline throughout the study period. [Table: 4]

Intraoperative sedation as compared by RSS was definitely higher in group-D from 5 minutes to 100 minutes but respiratory rate and SpO_2% were always comparable in both groups. [Table: 5] No significant difference of VAS score was found in postoperative period up to 24 hours except around 8th postoperative hour where VAS score was significantly lower in dexmedetomidine group (median 30 millimeter) in comparison to magnesium sulphate treated group (median 50 millimeter) (*p* value < 0.001). [Figure: 2]

Table 1: Comparison of demographic data between two groups

	Group D (n=37)	Group M(n=37)	*p* value
Peak sensory block height (Thoracic seg)	5.00(5.00-6.00)	6.00(6.00-7.00)	0.000
Time of Regression sensory block (min) [mean ± SD]	178.00±8.446	160±8.206	<0.001
Time of Regression motor block(min) [mean ± SD]	201.78±9.875	176.35±7.962	<0.001
Time of Rescue analgesia(min) [mean ± SD]	289.05±12.407	188.51±14.666	<0.001
Total diclofenac dose (mg) [mean ± SD]	150(75-150)	225(150-225)	<0.001

Table 2: Comparison of Peak sensory block height, Time of Regression sensory block, Time of Regression motor block, Time of Rescue analgesia and Total diclofenac dose between two groups

MINUTES	SBP (MEAN)			DBP (MEAN)			MAP (MEAN)			Heart rate (MEAN)		
	D	M	*p*	D	M	*p*	D	M	*p*	D	M	*p*
0	125.73	128.92	0.187	79.16	83.76	0.001	94.68	98.82	0.013	83.03	81.86	0.671
5	119.46	126.35	0.004	75.35	80.68	<0.001	90.05	95.90	<0.001	81.76	83.30	0.576
10	111.92	122.65	<0.001	73.11	79.08	<0.001	86.05	93.60	<0.001	78.32	81.78	0.215
15	106.30	121.35	<0.001	69.16	77.46	<0.001	81.59	92.09	<0.001	75.35	78.35	0.298
20	108.14	120.49	<0.001	71.22	76.84	<0.001	83.52	91.39	<0.001	76.08	78.27	0.446
40	110.24	120.78	<0.001	74.41	77.84	0.009	86.35	92.15	<0.001	73.84	76.81	0.283
60	113.62	121.24	<0.001	75.11	77.81	0.023	87.95	92.29	0.001	73.41	76.19	0.289
80	116.24	121.30	0.007	75.92	78.57	0.015	89.34	92.81	0.003	73.27	75.76	0.323
100	118.38	121.08	0.160	77.14	77.89	0.550	90.94	92.29	0.322	73.30	76.05	0.286
120	119.41	120.19	0.686	78.35	77.05	0.328	92.00	91.43	0.690	72.69	75.89	0.218

D- Group D M- Group M

Table 3: Comparison of intraoperative hemodynamic parameters between two groups

MINUTES	SBP (MEAN)			DBP (MEAN)			MAP (MEAN)			Heart rate (MEAN)		
	D	M	*p*	D	M	*p*	D	M	*p*	D	M	*p*
4	119.08	121.00	0.256	78.68	79.14	0.673	92.14	93.09	0.423	83.86	81.57	0.290
8	124.35	124.41	0.971	83.57	81.59	0.089	97.16	95.86	0.241	90.59	88.78	0.422
12	125.68	124.43	0.521	86.81	80.51	0.000	99.77	95.15	0.003	96.08	97.24	0.652
24	120.11	125.68	0.140	83.51	80.32	0.011	95.71	95.44	0.880	89.59	87.24	0.139

D- Group D M- Group M

Table 4: Comparison of postoperative hemodynamic parameters between two groups

MINUTES	SEDATION (MEAN)			RESPIRATORY RATE (MEAN)			SPO_2 (MEAN)		
	GROUP D	GROUP M	p	GROUP D	GROUP M	p	GROUP D	GROUP M	p
0	2.00	2.00	0.424	16.00	16.00	0.654	100.00	100.00	0.841
5	3.00	2.00	<0.001	14.00	14.00	0.779	100.00	100.00	0.424
10	3.00	2.00	<0.001	14.00	15.00	0.642	100.00	100.00	0.841
15	3.00	2.00	<0.001	14.00	14.00	0.611	100.00	100.00	0.650
20	3.00	2.00	<0.001	14.00	15.00	0.339	100.00	100.00	0.841
40	3.00	2.00	<0.001	14.00	14.00	0.250	100.00	100.00	0.841
60	3.00	2.00	<0.001	14.00	14.00	0.517	100.00	100.00	0.841
80	3.00	2.00	<0.001	14.00	15.00	0.189	100.00	100.00	0.689
100	2.00	2.00	0.005	14.00	15.00	0.593	100.00	100.00	0.549
120	2.00	2.00	0.110	15.00	16.00	0.059	100.00	100.00	0.841

Table 5 : Comparison of Depth of sedation (RSS), respiratory rate (rate/minute) and SpO_2 (percentage) between two groups

Figure 1

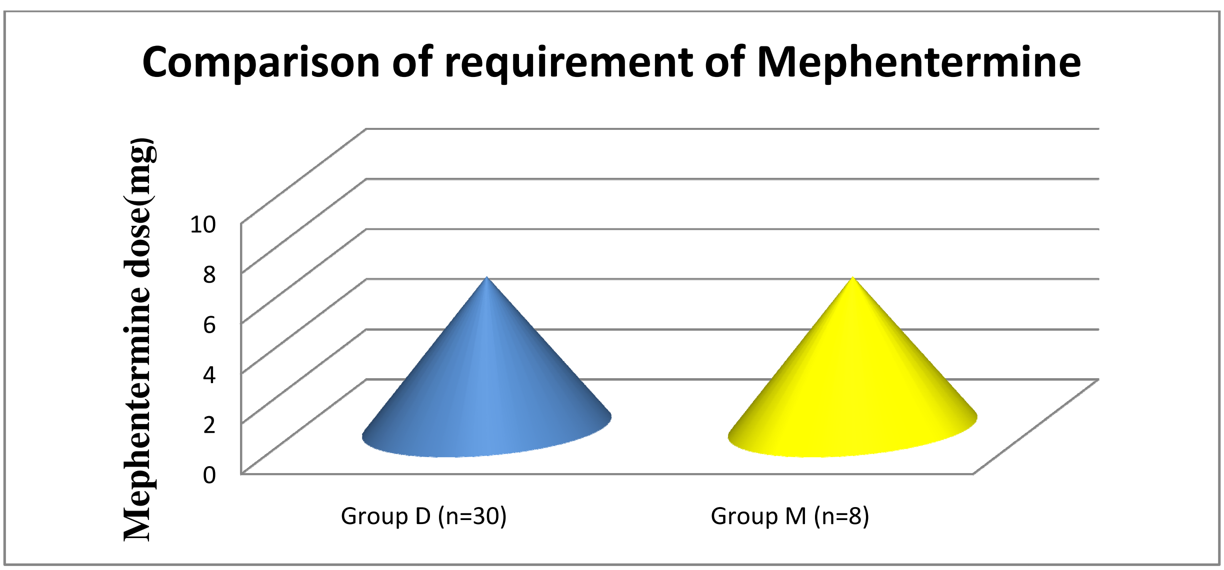

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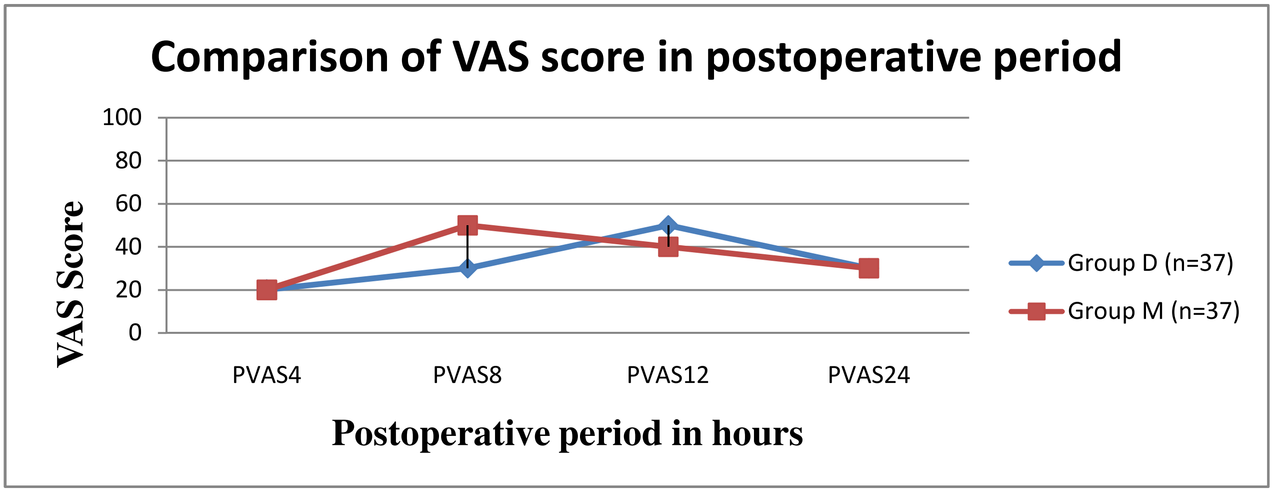
Figure 2



DISCUSSION

The use of magnesium sulfate as an adjuvant for perioperative analgesia is based on the properties of NMDA receptor antagonist and calcium channel blocker [15]. To decrease analgesic requirement it has been used in many routes like - intravenous in general anesthesia[10 ,11,12], intrathecal as adjuvent[17]. In addition, IV infusion of magnesium sulfate during spinal anesthesia were also reported[15,16]. These studies showed that IV magnesium sulfate infusion during surgery under spinal anesthesia reduces postoperative pain and analgesic consumption without any notable complications. Intravenous dexmedetomidine has been shown to reduce analgesic requirement during general [19] as well as spinal anaesthesia[20,21,22,23]. In the present study the analgesic efficacy of dexmedetomidine as premedication used intravenously before spinal anesthesia was compared with that of magnesium sulfate and found that single dose of IV dexmedetomidine before SAB increased the time until first request of analgesic for postoperative pain relief as well as decreased analgesic consumption in the first 24 hours postoperative period compared to IV magnesium sulfate in the patients undergone infraumbilical surgery. In addition, dexmedetomidine, in comparison to magnesium sulfate, prolonged the duration of motor blockade and increased the maximum upper level of sensory block without any significant adverse effect.

Synergistic interaction between dexmedetomidine and local anesthetics has been observed in previous studies [25]. Bolus followed by continuous infusion of intravenous dexmedetomidine has been reported to prolong sensory [20] as well as motor [21, 26] block duration in patients undergone surgery under spinal anesthesia. Recently, intravenous administration of a single bolus of 1 mcg/kg [22] and 0.5mcg/kg[23] were reported to prolong the duration of analgesia and sensory blockade.

The duration of sensory block and analgesia in the present study were found to be significantly increased in dexmedetomidine group than magnesium sulfate group. Total analgesic consumption in the first postoperative 24 hours period was less in dexmedetomidine group than magnesium sulfate

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group (p value <0.001). The underlying mechanism of this effect remains unclear. Dexmedetomidine has been shown to produce analgesic effects by acting at both spinal and supraspinal levels[27]. The effect seems to be mediated through both presynaptic and the post-synaptic alpha-2 receptors[28,29]. The direct analgesic, and/or vasoconstricting actions of dexmedetomidine are also suggested to be involved in this mechanism[30].

Postoperative VAS score in the first 8 hours was less in the dexmedetomidine group than magnesium sulfate group (p value PVAS8 < 0.001). After first 8 hours postoperative period the VAS score in the two groups was comparable.

Dexmedetomidine is most often delivered as an initial bolus followed by a continuous infusion. Initial bolus doses range from 0.5 to 1.0 μg/kg over 10 to 20 minutes, followed by a continuous infusion of 0.2 to 0.7 μ/kg/h[31]. Single dose of IV dexmedetomidine as premedication has also been reported to prolong spinal anesthesia [23]. In the present study single dose of dexmedetomidine has been used. As rapid administration of dexmedetomidine might produce tachycardia, bradycardia and hypertension [32] it was given slowly, over a period of 15 min.

Prolongation of motor blockade of spinal anesthesia with dexmedetomidine intravenous [20,21], intrathecal or intraperitoneal[33] has been reported. But in one study[23] use of a single dose of 0.5 mcg/kg of dexmedetomidine did not affect the duration of motor block. In the present study duration of motor blockade was prolonged significantly (p value <0.001) in dexmedetomidine group than the magnesium sulfate group. Earlier it was observed that effect of clonidine on motor blockade was concentration dependant[34] and the same theory might explain this phenomenon with dexmedetomidine as we have used a higher dose of dexmedetomidine (1 mcg/kg).

Hemodynamic response following dexmedetomidine infusion depends upon the dose and speed of infusion. A sequence of transient hypertension with reflex bradycardia, followed by hypotension is seen with higher dose and rapid infusion [35,36] .The subsequent decrease in blood pressure and heart rate may be due to decrease in central sympathetic outflow [36] . SBP, DBP, MAP were significantly less in group D than group M in the intraoperative period. However, the incidence of bradycardia in our study (in both the groups) was low and transient, only 2 patients in group D had bradycardia requiring atropine. This may be due to administration of drugs slowly over 15 min.

Most of the patients receiving dexmedetomidine were sedated, but easily arousable in the present study, but sedation score was significantly less in group M than group D during intraoperative period .Though few studies [20,22] showed excessive sedation in some patients who received dexmedetomidine, none of patients of either group had sedation score greater than 3 at any point of observation. Dexmedetomidine produces sedation by its central effect and seems to be dose dependant[37,38]. Lack of such effect may be the cause of decrease sedation in magnesium sulfate group.

In previous studies, it has been shown that dexmedetomidine caused no or minimal respiratory depression [38,39]. Desaturation was observed in one study[22] probably attributed to the advanced age of the patients. In the present study no respiratory depression was noted in any patients of either group.

Limitation:

Magnesium sulfate was taken as active comparator of dexmedetomidine to assess duration of postoperative

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analgesia. The efficacy of individual study drug regarding prolongation of bupivacaine induced sensory and motor block could not be evaluated as there was no normal saline control.

Conclusion

It can be concluded from the present study that pretreatment with single dose intravenous dexmedetomidine before subarachnoid block is more efficacious than single dose intravenous magnesium sulfate in providing postoperative analgesia by delaying time to first rescue analgesic requirement and also by decreasing total analgesic requirement in the first 24 hours postoperative period.

References

1. Morgan GE, Jr., Mikhail MS, Murray MJ, editors. Clinical Anesthesiology. 4th ed. New Delhi: Tata McGraw Hill; 2009. p.3.
2. Malhotra V, Sudheendra V, O'Hara J and Diwan S. Anesthesia and the Renal and Genitourinary systems. In: Miller RD, editor. Miller's Anesthesia. 7th ed. Philadelphia (PA): Churchill Livingstone Elsevier; 2010. p. 2119-21.
3. Koltka K, Uludag E, Senturk M, Yavru A, Karadeniz M, Sengul T, Ozyalcin S. Comparison of equipotent doses of ropivacaine-fentanyl and bupivacaine-fentanyl in spinal anesthesia for lower abdominal surgery. Anesthesia and Intensive Care. 2009; 37(6): 923-8.
4. Stephen M. Macres, Peter G. Moore, Scott M. Fishman.Acute Pain Management, in: Barash, Paul G.; Cullen, Bruce F.; Stoelting, Robert K.; Cahalan, Michael K.; Stock, M. Christine, editors. Clinical Anesthesia, 6th Edition. Philadelphia: Lippincott Williams & Wilkins;2009. p1482.
5. Subedi A, Biswas BK, Tripathi M, Bhattarai BK, Pokharel K. Analgesic effects of intrathecal tramadol in patients undergoing caesarean section: a randomised, double-blind study. Int J Obstet Anesth. 2013 Nov;22(4):316-21.
6. Ghai B, Makkar JK, Chari P, Rao KL. Addition of midazolam to continuous postoperative epidural bupivacaine infusion reduces requirement for rescue analgesia in children undergoing upper abdominal and flank surgery. J Clin Anesth 2009; 21: 113–9.
7. Strebel S, Gurzeler J, Scnider M, Aeschbach A, Kindler C. Small dose intratecal clonidine and isobaric bupivacaine for orthopaedic surgery: a dose response study.AnaesthAnalog 2004; 99:1231-8.
8. Kanazi GE, Aouad MT,Jabbour-Khoury SI et al. Effect of low dose dexmedetomidine or clonidine on the characteristic of bupivacaine spinal block. ActaAnasthesolScand 2006; 50:227-7.
9. Mahmud M Al. Mustafa.Sami A . Abu-Halaweb,Abdel Karim S Alowedi,Michael M Ramsey. Effect of low dose dexmedetomidine added to spinal bupivacaine for urological procedures . Saudi Med J2009.Vol 30(3).
10. Tauzin-Fin, P.; Sesay, M.; Delort-Laval, S.; Krol-Houdek, M. C.; Maurette, P. Intravenous magnesium sulphate decreases postoperative tramadol requirement after radical prostatectomy Eur J Anaesthesiol 2006 December;23(12): 1055-9.
11. Ray M, Bhattacharjee DP, Hajra B, Pal R, Chatterjee N. Effect of clonidine and magnesium sulphate on anaesthetic consumption, haemodynamics and postoperativerecovery: A comparative study**.** Indian J anaesth 2010 Mar;54(2):137-41.
12. Kara, H.; Şahin, N.; Ulusan, V.; Aydoğdu, T. Magnesium infusion reduces perioperative pain. Eur J Anaesthesiol 2002 Jan; 19(1): 52-6.
13. Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg 1998; 87: 206-10.

14. Levaux Ch, Bonhomme V, Dewandre PY, Brichant JF, Hans P. Effect of intra- operative magnesium sulphate on pain relief and patient comfort after major lumbar orthopaedic surgery. Anaesthesia 2003; 58: 131-5.
15. Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS, Do SH. I.V. infusion of magnesium sulphate during spinal anaesthesia improves postoperative analgesia. Br J Anaesth 2010; 104: 89-93.
16. Apan A, Buyukkocak U, Ozcan S, Sari E, Basar H. Postoperative magnesium sulphate infusion reduces analgesic requirements in spinal anaesthesia. Eur J Anaesthesiol 2004; 21: 766-9.
17. Hamad Sanad, Tarek Abdelsanam, Mohamad Hamada, Mohamad Abdel M. Onem, Alsherbiny. Effects of adding magnesium sulphate, midazolam or ketamine to hyperbaric bupivacaine for spinal anesthesia in lower abdominal and lower extremity surgery. Ain Sham J of Anesthesiol 2010;3(1).
18. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991; 44: 293-9.
19. Unlugenc H, Gunduz M, Guler T, Yagmur O, Isik G. The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. Eur J Anaesthesiol 2005 May;22(5):386-91.
20. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem SM. Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East J Anesthesiol. 2009;20:225–31.
21. Elcicek K, Tekin M, Kati I. The effects of intravenous dexmedetomidine on spinal hyperbaric ropivacaine anesthesia. J Anesth. 2010;24:544–8.
22. Hong JY, Kim WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia in elderly patients. Acta Anaesthesiol Scand. 2012;56:382–7.
23. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth. 2010;57:39–45.
24. Morgan GE, Jr., Mikhail MS, Murray MJ, editors. Clinical Anesthesiology. 4th ed. New Delhi: Tata McGraw Hill; 2009. p.899.
25. Memis¸ D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004; 98: 835–40.
26. Lugo VW, Gomez IA, Cisneros-Corral R, Martinez-Gallegos N. Intravenous dexmedetomidine versus intravenous clonidine to prolong bupivacaine spinal anaesthesia. A double blind study. Anestesia en Mexico. 2007;19:143–6.
27. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth 2002; 88:669-675.
28. Jorm CM, Stamford JA. Actions of the hypnotic anaesthetic, dexmedetomidine, on noradrenaline release and cell firing in rat locus coeruleus slices. Br J Anaesth. 1993;71:447–9.
29. Guo TZ, Jiang JY, Buttermann AE, Maze M. Dexmedetomidine injection into the locus ceruleus produces antinociception. Anesthesiology. 1996;84:873–81.
30. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93: 382–94.
31. Simon C. Hillier, Michael S. Mazurek. Monitored Anesthesia Care. In: Barash, Paul G.; Cullen, Bruce F.; Stoelting, Robert K.; Cahalan, Michael K.; Stock, M. Christine, Editors. Clinical Anesthesia. 6th Edition. Philadelphia: Lippincott Williams & Wilkins;2009. p.825.
32. Grant SA, Breslin DS, Macleod DB, Gleason D, Martin G. Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. J Clin Anesth 2004; 16:124-6.

33. Calasans-Maia JA, Zapata-Sudo G, Sudo RT. Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs. J Pharm Pharmacol 2005; 57: 1415–20.
34. Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. Acta Anaesthesiol Scand. 2003;47:1001–5.
35. Mason KP, Zurakowski D, Zgleszewski S, Prescilla R, Fontaine PJ, Dinardo JA. Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric MRI. Paediatr Anaesth. 2010;20:516–23.
36. Sudheesh K, Harsoor S. Dexmedetomidine in anaesthesia practice: A wonder drug? Indian J Anaesth. 2011;55:323–4.
37. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992;77:1125–33.
38. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000; 90: 699–705.
39. Jaakola ML. Dexmedetomidine premedication before intravenous regional anesthesia in minor hand surgery. J Clin Anesth. 1994 May- Jun; 6(3): 204-11.