Comparative evaluation of clinical efficacy of dexmedetomidine when used in intravenous or intrathecal routes during spinal anaesthesia

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Abstract

Introduction: Spinal anaesthesia is the anesthesia of choice for patients undergoing lower abdominal and lower limb surgeries. However its use is restricted by the limited duration of its action.

Aim: To study the comparative evaluation of clinical efficacy of dexmedetomidine when used either by intravenous or intrathecal route in patients undergoing surgeries under spinal anaesthesia.

Materials and Methods: 60 American Society of Anaesthesiologists Grade I and II were randomized to receive dexmedetomidine by either intravenous (0.5µgm/kg) (Group I) or intrathecal (0.5µgm) (Group II) routes, in patients scheduled for surgeries under spinal anaesthesia. Primary outcomes studied were the duration of sensory and motor blocks. Secondary outcomes were the time for first request of analgesia, sedation levels and incidence of bradycardia and hypotension.

Results: Group II patients showed significant prolongation of sensory and motor block as compared to Group I (p= 0.009, <0.000 respectively). Similarly the time of rescue analgesia is greater in Group II (p= 0.0001). However mean sedation levels were greater in Group I (p=0.02). There was no significant difference in the incidence of bradycardia and hypotension between two groups.

Conclusion: Intrathecal dexmedetomidine as an adjuvant in spinal anaesthesia, showed significant prolongation of duration of sensory and motor blocks as compared to its intravenous counterpart, without significant increase in incidence of adverse effects.

Keywords: Dexmedetomidine, Intravenous, Intrathecal, Adjuvant, Spinal anaesthesia.

Introduction

Anaesthesia, since its first successful demonstration in 16 October 1846 at Massachusetts General Hospital, has witnessed countless advancements and inventions.[1] Spinal or intrathecal anaesthesia, the anaesthesia of choice for lower abdominal and lower limb surgeries, has also undergone innumerable innovations pertaining to the drugs and devices. To overcome its limited duration of action, different adjuvants have been used to prolong the duration of intrathecal block, with varied results.[2,3] Dexmedetomidine, a highly selective α_2-adrenoceptor agonist, has been used for premedication and as adjuvant to general anaesthesia.[4] Although a synergistic interaction between intrathecal dexmedetomidine and local anaesthetics has been observed in previous studies, there are no clinical data regarding the effects of intravenous dexmedetomidine premedication on spinal anaesthesia.[5] Hence we undertook this study to evaluate the comparative differences in characteristics of spinal anaesthesia when dexmedetomidine was given by either of the two different routes as an adjuvant - intravenous or intrathecal, in patients undergoing surgeries under spinal anaesthesia.

Materials and Methods

This clinical, randomized, double-blind study was undertaken in Santosh Hospital, Ghaziabad in the duration between 2014-2016. To calculate the sample size, a power analysis of alpha= 0.05 and beta = 0.80, showed that 23 patients per study group were needed for 20% difference in sensory regression to two dermatomes. To compensate for the drop-outs and to further increase the power of the study, we enrolled 30 patients in each group. After taking institutional ethical clearance and informed consent, 60 American society of Anaesthesiologist grade I and II patients scheduled for lower abdominal and lower limb surgeries under spinal anaesthesia were randomly divided into two groups of 30 patients each. Group I included intravenous dexmedetomidine given before the initiation of spinal anaesthesia in the doses of 0.5µgm/kg slow over the period of 10 minutes. Group II included dexmedetomidine 0.5 µgm given via spinal route.

Exclusion criteria included contraindication to spinal anaesthesia; patients on α2-adrenoceptor antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitors; patients having abnormal cardiac rhythm; patients with diabetes, hypertension or other systemic co-morbid conditions.

After obtaining pre-anaesthetic clearance, patients were randomly allocated into two groups. Randomization was done with opaque sealed envelopes using computer generated randomization sequence. On the day of operation, after checking all the preoperative protocols, patients were wheeled into the operation theater and all the necessary monitoring parameters were attached, which included pulse oximetry, electrocardiogram, and non-invasive blood pressure. Patients were preloaded with intravenous ringer lactate

at 15ml/kg. Patients in Group I were given intravenous dexmedetomidne 0.5µgm/kg diluted to 10ml normal saline slow over the period of 10 minutes followed by intrathecal 2.5ml 0.5% bupivacaine heavy diluted with 0.5ml normal saline to the total volume of 3ml. Patients in Group II were given same volume normal saline over the period of 10 minutes intravenous followed by intrathecal administration of 2.5ml of 0.5% heavy bupivacaine with 0.5µgm of dexmedetomidine diluted to 0.5ml to make the total volume of 3ml for spinal administration. There was a waiting period of 5 minutes after the end of intravenous infusion and spinal anaesthesia administration. Spinal anaesthesia was given in sitting position with 26 gauze quincke-babcock spinal needles. The study drugs were prepared by anaesthesiologist who was no further involved in the management of case. The readings were recorded by another anaesthesiologist who was not aware of the nature of the study drug administered and who was also the in-charge of the case. Patients were also unaware of the study group allocation. Hence study proceeded in a double blind fashion. Intraoperatively, fluids were administered according to the institutional protocol. Oxygen was supplemented at the rate of 2l/minute to all the patients. Operation was allowed to commence after the demonstration of adequate block. All the haemodynamics and other additional drugs administered were recorded. Intraoperative bradycardia and hypotension were recorded and managed according to the institutional protocols.

For the comparative evaluation, following parameters were recorded. Maximum level of sensory block was recorded using loss of pin-prick sensation in the mid-clavicular line. Duration of sensory block was recorded by assessing the time taken from the onset of sensory block to regression to two dermatomes lower from the highest dermatomal level achieved. Postoperative analgesia was given on demand and time for first request of analgesia was recorded. Motor block was assessed using modified bromage scale (0 = no paralysis, 1 = unable to raise the extended leg, 2 = unable to flex knee, 3 = unable to flex ankle). Duration of motor block was recorded as the time taken to reach bromage scale 0 from the maximum motor block. Sedation was assessed one hour after the study drug administration using Ramsay Sedation Scores (1 = anxious and agitated, 2 = cooperative and tranquil, 3 = drowsy but responsive to command, 4 = asleep but responsive to glabellar tap, 5 = asleep with sluggish response to tactile stimulation, 6 = asleep and no response). Bradycardia was defined as heart rate less than 50 beats/minute and hypotension was defined as systolic blood pressure less than 80mmHg. Intraoperative episodes of bradycardia and hypotension were recorded.

Statistical evaluation was done using Epi-info 7. T-test was used for continuous variables and Chi-square test was used for categorical variables. Data was presented as Mean ± SD or as percentage. P value less than 0.05 was considered significant.

Results

Out of 60 patients, one patient in Group I (intravenous dexmedetomidine group) had to be dropped out because of the failed spinal anaesthesia and general anaesthesia had to be administered. All the patients in Group II (intrathecal dexmedetomidine group) completed the study. The two groups were comparable with respect to age, weight, gender distribution. The demographic profile of the patients is given in table 1.

Table 1: Patient characteristics

S. No.	Patient characteristic	Group I (n = 29)	Group II (n = 30)
1	Age	36.55 ± 12.91	40.15 ± 13.62
2	Weight	60.77 ± 8.36	57.53 ± 7.24
3	Sex (male: female)	13 : 16	16 : 14

Values as Mean ± SD or ratio

There was no significant difference in the maximum mean sensory block levels attained in two groups. It was 7.21±1.99 in Group I, while in Group II it was 6.7±1.95 (p=0.32). However there was significant difference in the mean duration of two segment sensory regression (p= 0.009). Similarly time for request of first analgesia was significantly greater in Group II as compared to Group I (p=0.0001). Motor block characteristics also showed trend similar to that of sensory block. The duration of motor block was significantly greater in Group II. Characteristics of sensory and motor block are shown in table 2.

Table 2: Sensory and motor block characteristics

S. No.	Block characteristics	Group I	Group II	P value
1	Maximum sensory block level	7.21 ± 1.99	6.7 ± 1.95	0.32
2	Time to two dermatome sensory regression	140.52 ± 54.58	198 ± 70.87	0.009
3	Time for first request of analgesia	191.86 ± 33.91	233.4 ± 41.20	0.0001
4	Recession to Bromage Scale 0	185.76 ± 28.87	268.33 ± 65.18	<0.000

Values as Mean ± SD

Mean sedation levels assessed 1 hour after spinal anaesthesia were greater in Group I (3.33 ± 1.0613) as compared to Group II (2.67 ± 1.045) (p=0.02).
5 (17%) patients had bradycardia in Group I, while it was 4 (13%) in Group II (p= 0.73). Bradycardia was treated with injection atropine 0.6mg intravenous. Incidence of hypotension was same in both the groups (13%).

Discussion

Dexmedetomidine (DEX), a selective α-2 adrenergic agonist, is an excellent drug for sedation in intubated as well as non-intubated patients in critical care and for short procedures. Sleep induced with dexmedetomidine is termed co-operative sleep, and the drug does not disturb sleep architecture, as well as, the respiratory drive.[6.7]

α-2 adrenergic receptors are found in many sites throughout the body including central nervous system, spinal, and peripheral tissues. In CNS, the highest densities of α-2 adrenergic receptors are found in locus coeruleus, an important modulator of vigilance. Presynaptic activation of α-2 adrenoceptors in the locus coeruleus inhibits the release of norepinephrine and results in the sedative and hypnotic effects. Furthermore, the locus coeruleus is the site of origin for descending medullospinal noradrenergic pathway. Stimulation of the α-2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. At the spinal cord, stimulation of α-2 adrenergic receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the release of substance P. Furthermore, α-2 adrenergic adrenoceptors located at the nerve endings have possible role in the analgesic mechanism of α-2 agonist by preventing norepinephrine release. The spinal mechanism is the principal mechanism for analgesic action of DEX even though there is a clear evidence for both a supraspinal and peripheral sites of action.[2,8,9]

We had significantly greater prolongation sensory and motor block in Group II (intrathecal dexmedetomidine) as compared to the Group I (intravenous dexmedetomidine) (p= 0.009, p= <0.000 respectively). The time for first request of analgesia was also 191.86±33.91 in Group I as compared to Group II 233.4 ± 41.20 (p= 0.0001). Also there was greater incidence of sedation in Group I (p= 0.02). However, the incidence of bradycardia and hypotension showed no significant difference in the two groups.

In accordance with our study, Kaya had also reported the time for sensory regression of two dermatomes (from maximum level) with intravenous DEX as 145 ± 26min.[5] The time to two-segment sensory regression with intrathecal DEX was 198 ± 70.87 minutes in our study. Al-Mustafa has reported sensory regression time to S1 dermatome to be 277.1 ± 23.2minutes with intrathecal DEX.[10] This duration is longer than that reported in our study, due to the fact that they have taken sensory regression to S1 dermatome, while we studied sensory regression to only two segments lower than the maximum dermatome achieved. However our results contrast with those of Gupta and Mahendru.[11,12] This could be due to the fact that they had better premedicated their patients. Premedication allays anxiety, produces light sedation and some analgesia, resulting in block prolongation.

The maximum sensory level obtained was higher in intrathecal group in our study. Our results compliment those of other authors.[11] In contrast, the results of mean maximum sensory level obtained with intravenous DEX in our study did not match with those of other studies.[5] The type of study subject selection could be one of the reasons of this variation, with some patients requiring more trendelenburg position, while others requiring neutral table position. However, sensory levels of intravenous DEX simulated those by other studies.[8]

We had significant difference in the mean time for first request of analgesia in two groups (p=0.0001). Our study simulates the study by Mahendru et al, who have reported similar rescue analgesia time with intrathecal DEX.[12] The time for first request of analgesia with intravenous DEX was contrast to that of Hong et al.[13] It was shorter in the present study. They had used the doses double to that used in our study. Also the nature of surgery could be the probable reason, with our patients undergoing lower abdominal and lower limb surgeries, which resulted in more tissue trauma and hence early and more severe onset of pain.

Kaya had similar findings of duration of motor block regression with intravenous DEX as compared to our results.[5] Lee has also reported motor block duration as 132.9 ±43.4 min.[8] Our results of motor regression with intrathecal DEX are comparable with Al-Mustafa and Kanzi.[10,14] However Gupta R et al have reported longer duration of motor block with intrathecal DEX. Probably the reason is similar to that given with sensory block prolongation.[11]

The mechanism by which intrathecal α_2-adrenoceptor agonists prolong the motor and sensory block of local anaesthetics is not clear. It may be additive or synergistic effect secondary to the different mechanisms of action of the local anaesthetic and the α_2-adrenoceptor agonist. The local anaesthetics act by blocking the sodium channels, whereas the α_2-adrenoceptor agonist act binding to presynaptic C-fiber and post-synaptic dorsal horn neurons. Intrathecal α_2-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of pure-synaptic dorsal horn neurons. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anesthetics. Intrathecal α_2-adrenoceptor agonists have been found to have antinociceptive action for both somatic and visceral pain. The prolongation of motor block of spinal anesthetics may result from the binding

of α_2-adrenoceptor agonists to motor neurons in the dorsal horn.[10,11,15] Mechanism of intravenous dose is unclear. However, supraspinal, direct analgesic and vasoconstrictive activities are involved in the mechanism. Moreover, DEX produces greater degree of differential block by preferentially blocking myelinated A-α fibers involved in sensory conduction than unmyelinated C-fibers involved in motor conduction.(8)

Similar to our study, other studies have also reported prolongation of both motor and sensory block when DEX was used as an adjuvant with local anaesthetics.(15,16)

There is increased incidence of bradycardia with DEX. This is due to decrease in plasma chatecholamine levels sympathetic outflow by a2- adrenergic activation. The incidence is higher in various other studies, where loading dose followed by continuous infusion is used.(8) The incidence of bradycardia was 5 in our study in Group I, while it was 4 in the Group II. Lee had reported lower incidence with intravenous DEX. The lesser number of patients in their study could be reason for it. The incidence of hypotension was not significantly different in our two study groups.

DEX is an excellent drug for sedation in intubated as well as non-intubated patients in critical care and for short procedures. Sleep induced with DEX is termed co-operative sleep, and the drug does not disturb sleep architecture, as well as, the respiratory drive.(2,4,6)

Sedation is a known property of DEX. Infect it is used as a sedation agent in intensive care unit.(4,6,10) We reported significantly greater mean sedation scores in intravenous Group I as compared to Group II in first hour. Our results are in accordance with those of other authors.(2,5,8,10,11)

The meta-analysis by Niu showed that DEX prolonged the duration of spinal anaesthesia and improved postoperative analgesia. The occurrence of hypotension and side-effects was not significantly different between DEX and placebo.(16)

Conclusion

Dexmedetomidine, a selective α_2-adrenoceptor agonist, having short half-life, can be used effectively as an adjuvant to prolong the duration of spinal anaesthesia. It is an excellent drug for perioperative sedation when used via intravenous route. Relative lack of side effects has resulted in its use in not just perioperative setting, but also in intensive and critical settings to provide a favorable level of anxiolysis along with sympatholysis.

References

1. Chaturvedi R, Gogna RL. Ether day: an intriguing history. Med J Armed Forces India 2011;67:306-8.
2. Kubre J, Sethi A, Mahobia M, Bindal D, Narang N, Saxena A. Single dose intravenous dexmedetomidine prolongs spinal anesthesia with hyperbaric bupivacaine. Anesth Essays Res 2016;10:273-7.
3. Seth BS, Samuel M, Shreevastav D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anaesth 2007;51:415-9.
4. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. Curr Opin Anaesthesiol 2008;21:457-61.
5. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurpert A, Mogol EB, et. al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Canad J Anesth 2010;57(1):39-45.
6. Kamibayashi T, Maze M. Clinical uses of Alpha-2 adrenergic agonists. Anethesiol 2000;93:1345-9.
7. Arian SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. Anesth Analg 2002;95:461-6.
8. Lee MH, Ko JH, Kim EM, Cheung MH, Choi YR, Choi EM. The effect of intravenous dexmedetomidine on spinal anaesthesia: comparison of different doses of dexmedetomidine. Koren J Anesthesiol 2014;67(4):252-7.
9. Ishii H, Kohno T, Yamakura T, Ikoma M, Baba H. Action of dexmedetomidine on subsantia gelatinosa neorons of the rat spinal cord. Eur J Neurosci 2008;27:3182-90.
10. Al-Mustafa MM, Abu-Halaweb SA, Aloweidi AK, Murshidi MM, Ammari BA, Awwad ZA., et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi Med J 2009;30:365-70.
11. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. J Anaesthesiol Clin Pharmacol 2011;27(3):339-343.
12. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric Bupivacaine for lower limb surgeries: A double blind controlled study. J Anaesthesiol Cl Pharma 2013;29(4):496-502.
13. Hong JY, Kim WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia. Act Anaesthesiol Scand 2012;56(3):382-7.
14. Kanzi GE, Aouad MT, Jassons-Knoury SI, AlJazzar MD, Alameddin MM, Al-Yaman, et al. Effect of low-dose dexmedetomidine and clonidine on characteristics of bupivacaine spinal block. Acta Anesthesiol Scandinavica 2006;50(2):22-7.
15. Gupta R, Bogra J, Verma R, Kohli M, Kumar S. Dexmedetomidine as intrathecal adjuvant to postoperative analgesia. Ind J Anaesth 2011;55(4):347-51.
16. Niu XY, Ding XB, Guo T, Chen MH, Fu SK, Li Q. Effects in intrathecal and intravenous dexmedetomidine in spinal anaesthesia: a meta-analysis. CNS Neurosci Ther 2013;19(11):897-904.