Determination of Optimal Dose of Intrathecal Dexmedetomidine

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Summary
Role of dexmedetomidine as adjuvant to intrathecal local anaesthetics is being increasingly described in the literature. This prospective, double blind, randomised study evaluated various doses of dexmedetomidine with an aim to find out the dose of dexmedetomidine. Patients undergoing elective vaginal hysterectomy were randomly divided into 5 groups of 16 patients each. Group 1 (control) received 3 ml of 0.75% isobaric ropivacaine. Group 2, 3, 4 and 5 received additional 3, 5, 10 and 15 μg dexmedetomidine respectively. Compared to control, onset of sensory block was quickened in all in groups except in group 2, while onset of motor block was quickened in all groups except groups 2 and 3. Sensory 2 segment regression, regression of sensory block to S2, time to regression of motor block to modified Bromage score 0 and time to 1st analgesic request was prolonged in all the test groups. Maximum Visual analogue score and total postoperative analgesic requirement was lower in all test groups when compared to control. No difference was observed between group 4 and 5 when they were compared in terms of onset or duration of sensory and motor block or post-operative analgesia. However, group 5 had higher incidence of hypotension and bradycardia and required higher dose of ephedrine and atropine than other groups. Dexmedetomidine in a dose of 10 μg is preferable to other doses in terms of balance between potentiation of subarachnoid block and development of undesirable effects.
Keywords: *dexmedetomidine, spinal anesthesia, dose, anesthesia.*

Introduction
Lower abdominal surgeries are commonly performed under spinal anaesthesia. Many adjuvants have been used improve the quality of intraoperative sensory and motor block characteristics as well as postoperative analgesia.

These include, but are not limited to opioids, neostigmine, midazolam, ketamine, magnesium and α_2 agonists.[1-4] Use of clonidine, a α_2 agonist, is well established for potentiating the motor and sensory effects of intrathecally administered local anaesthetics.[1,5] Use of dexmedetomidine, a

newer, selective α₂ agonist (8 times more selective for α₂ receptors than clonidine) is being is being increasingly described in the literature as an adjuvant for spinal anesthesia.[5,6] Various doses ranging from 3 to 15 µg has been used in human studies without any significant adverse effects including neurotoxicity.[5,7-9] Intrathecal administration of up to 100 µg dexmedetomidine has not shown any signs of neurotoxicity in animals.[10] Till date, there is no study which establishes optimal dose of intrathecal dexmedetomidine.

This study was designed with the aim to find out the dose of dexmedetomidine which optimally potentiates the effects of intrathecal bupivacaine without significantly increasing the adverse effects. We compared 4 different doses of dexmedetomidine (3, 5, 10 and 15 µg) with control as an adjuvant to ropivacaine in patients undergoing elective vaginal hysterectomy.

Materials and Methods

This prospective, double blind, randomised study was conducted after getting approval of ethical committee. After taking informed consent, patients belonging to ASA physical status I or II and undergoing elective vaginal hysterectomy were enrolled in this study. Exclusion criteria were refusal for consent, contraindication for spinal anaesthesia, patients on analgesic, allergy to study medications, and neurological diseases.

All patients received oral diazepam 0.2 mg/kg on the night before surgery. The monitors were applied for monitoring (heart rate, non-invasive blood pressure, SPO₂, temperature and ECG). Before the intrathecal injection, ringer lactate 15 ml/kg body weight was infused to preload the intravascular compartment.

Using computer generated random numbers; the patients were divided into 5 groups (Group 1: control, Groups 2-5: test group) and were given following intrathecal medications: Group 1 received 3 ml of 0.75% isobaric ropivacaine, group 2 received 3 ml of 0.75% isobaric ropivacaine + 3 µg dexmedetomidine, group 3 received 3 ml of 0.75% isobaric ropivacaine + 5

µg dexmedetomidine, group 4 received 3 ml of 0.75% isobaric ropivacaine + 10 µg dexmedetomidine and group 5 received 3 ml of 0.75% isobaric ropivacaine + 15 µg dexmedetomidine. Normal saline was added to all the study solutions to obtain a final volume of 3.2 ml. The study solution was prepared by an anaesthesia technician not involved in the patient's care. The patients, anaesthesiologist who delivered the drug and the observing anaesthesiologist were blind to the study solution and study group. With all aseptic precautions, a midline spinal puncture was performed at L3/4 interspace with 25G pencil point needle with hole in the spinal needle facing upward and the patients in the sitting position and the anaesthetic solution was injected over 10-15 seconds without barbotage or aspiration. Patients were returned to supine position immediately after completion of intrathecal drug administration. Surgery was started 20 minutes after the intrathecal drug administration. Bilateral sensory dermatomal block obtained was assessed by loss of pinprick sensation to 23 G hypodermic needle in midclavicular line every two minutes for 20 minutes, after which it was assessed every 20 minutes till sensory block had regressed to S2. Motor block was assessed every two minutes for 20 minutes and then every 20 minutes after surgery till full motor recovery using modified Bromage scale.[11] Sedation was assessed using a five-point scale (1-alert and wide awake, 2-arousable to verbal command, 3-arousable with gentle tactile stimulation, 4-arousable with vigorous shaking and 5-unarousable) every 20 minutes till conclusion of surgery.[11] Postoperative pain was assessed every hour using Visual analogue scale (VAS).

Following recordings were noted: peak sensory level achieved, time taken to block T10 sensory dermatome, 2 segment regression from peak sensory block, regression of block to S2, time taken to achieve modified Bromage 3, full motor recovery (defined as modified Bromage 0) and time taken to first analgesic request, maximum

sedation score, maximum VAS score and total analgesic consumption.

Complications were treated as follows: hypotension (systolic blood pressure of <90 mm Hg) was treated with increments of 5mg ephedrine, bradycardia (heart rate of <50 bpm) was treated with increments of 0.3 mg atropine, and respiratory depression (SPO_2<90% on room air) was treated with oxygen via Hudson's face mask. Adverse events (hypotension, bradycardia, respiratory depression, sedation, dry mouth, shivering, pruritus nausea and vomiting) were recorded during operation and recovery. Postoperative pain relief, when demanded by patient was given with 1 gm of intravenous paracetamol.

A sample size of 16 patients per group was determined through power analysis ($\alpha = 0.05$; $\beta = 0.80$) to detect an increase of 30 minutes in the time of a two-dermatome sensory regression with a standard deviation of 30 minutes. More than two continuous parametric variables were analyzed using Analysis of Variance followed by Tukey's post hoc test. Kruskal-Wallis test was used to analyze non-parametric continuous and ordinal data. Discrete variables were compared using Chi-square test. A p value<0.05 was considered significant. Data is being expressed as mean ± Standard deviation, median or number/ percentages as appropriate.

Results

Sixteen patients were studied in each group. No patient was excluded from the study. Groups were statistically comparable with respect to baseline characterstics (Table 1).

The sensory and motor block characteristics are compared in Table 2. The median of peak sensory block achieved ranged from T4 to T5 sensory dermatome and was statistically similar among the groups.

Compared to control, the time to achieve T10 sensory block was significantly reduced in groups 3, 4 and 5. This duration was statistically similar between group 1 and 2; and between group 4 and 5. The comparison among other groups showed significantly different durations, with the group receiving higher dose of dexmedetomidine having lower time to achieve T10 sensory block.

Compared to control, the time taken to achieve modified Bromage 3 was significantly lower in all other groups except in group 2 and 3, in which the difference was statistically insignificant. The difference was not significant when comparison was made between groups 4 and 5. For comparison among all other groups, the group which received higher dose of dexmedetomidine had significantly lower times to achieve modified Bromage 3.

Sensory 2 segment regression, regression of sensory block to S2, time of regression of motor block to Bromage 0 and time to 1st analgesic request was significantly increased in all the groups as compared to control. However, these durations were not significantly increased when comparison was made between group 4 and group 5. Comparison between other groups revealed that these durations were significantly increased in groups using higher dose of dexmedetomidine.

Mean of maximum VAS scores and total postoperative analgesic requirements were significantly lower in all groups as compared to control. However, the VAS scores and analgesic requirements were statistically similar in groups 4 and 5. Comparison among other groups showed that mean VAS score and analgesic requirements were lower in groups receiving higher dose of dexmedetomidine.

Side effects are summarised in Figure 1. Incidence of hypotension and bradycardia was significantly increased in group 5. Accordingly, total dose of ephedrine and atropine was significantly high in group 5. Level of sedation was statistically similar in all the groups. None of the patients complained of respiratory depression, dry mouth, shivering, nausea and vomiting.

Table 1: Comparison of baseline and demographic characteristics

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)	Group 5 (n=16)	p
Age	50.13±10.84	46.31±10.61	45.63±7.46	47.19±11.74	45.44±8.56	0.6730
Weight	65.69±6.85	63.44±6.26	66.69±7.94	62.56±9.87	60.25±8.17	0.1661
Height	163.19±5.89	164.50±8.49	167.75±6.96	165.38±5.07	165.63±8.56	0.479
ASA I:II	5:11	4:12	9:7	8:8	10:6	0.1487
Duration of surgery	106.44±9.62	105.25±10.11	101.25±8.27	111.13±11.74	107.81±11.49	0.1096

Table 2 : Comparison of sensory and motor block characteristics

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)	Group 5 (n=16)	p
Median of Peak sensory block	T4	T5	T4	T4	T4	0.6527
Time to T10 block	$6.69±1.99^{+†‡}$	$6.44±1.46^{^Ω\$}$	$4.69±1.96^{\#@}$	3.06±0.93	2.94±0.85	<0.0001
2 Segment regression	$88.75±14.55^{*+†‡}$	$109.06±16.55^{^Ω\$}$	$137.50±16.12^{\#@}$	156.25±20.94	161.25±15.44	<0.0001
Regression to S2	$198.75±19.96^{*+†‡}$	$298.13±23.73^{^Ω\$}$	$383.75±24.46^{\#@}$	417.50±36.42	438.75±38.28	<0.0001
Time to modified Bromage 3	$9.31±1.01^{†‡}$	$8.38±1.63^{Ω\$}$	$7.69±2.57^{\#@}$	3.94±0.93	3.88±1.59	<0.0001
Regression to modified Bromage 0	$147.5±10.00^{*+†‡}$	$317.5±25.17^{^Ω\$}$	$396.25±40.80^{\#@}$	438.75±33.84	458.75±23.63	<0.0001
1st analgesic request	$180.81±21.71^{*+†‡}$	$310.19±49.68^{^Ω\$}$	$387.13±30.98^{\#@}$	429.31±27.04	450.94±29.97	<0.0001
Maximum VAS	$7.75±0.86^{*+†‡}$	$6.19±0.91^{^Ω\$}$	$4.81±1.05^{\#@}$	3.38±1.67	3.25±1.29	<0.0001
Total analgesics required	$3.81±0.40^{*+†‡}$	$2.13±0.62^{^Ω\$}$	$1.38±0.72^{\#@}$	0.50±0.82	0.44±0.63	<0.0001

Statistically significant: * =Group 1 vs Group 2, +=Group 1 vs Group 3, †= Group 1 vs Group 4, ‡= Group 1 vs Group 5, ^= Group 2 vs Group 3, Ω= Group 2 vs Group 4, \$=Group 2 vs Group 5, #=Group 3 vs Group 4, @=Group 3 vs Group 5

Figure 1: Comparison of adverse effects (* denotes significant difference, p<0.05)
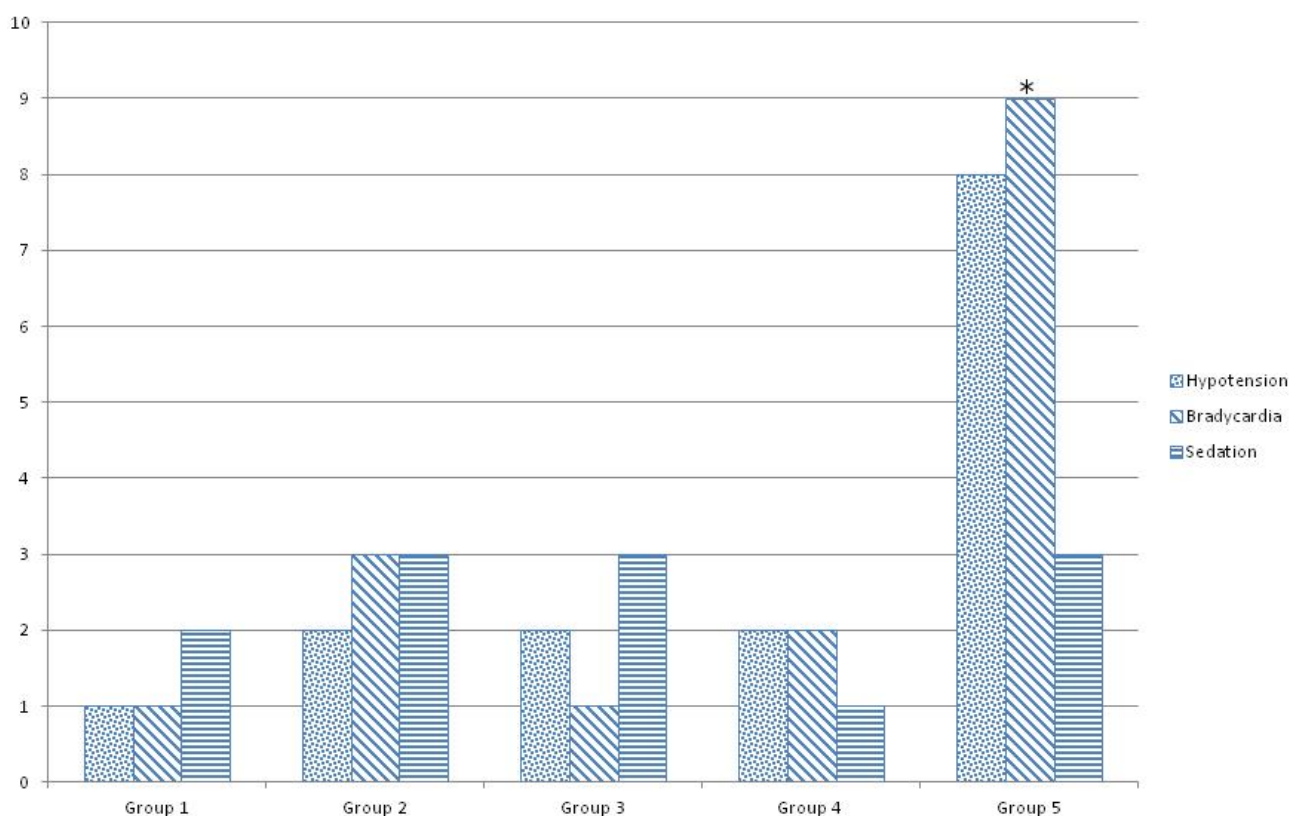
Discussion

Use of intrathecal adjuvants has gained popularity for prolonging the duration of motor and sensory block, better success rate and analgesia. Exact mechanism by which intrathecalα_2 agonists potentiate the motor and sensory block of intrathecal local anaesthetics is not well known.[5] Local anaesthetics act on neurons by blocking sodium channels while α_2 agonists act on presynaptic C fibres, where they decrease the release of neurotransmitters and in dorsal horn, where they hyperpolarize postsynaptic neurons. Potentiation of sensory and analgesic effect of local anaesthetics may be attributed to agonist action of α_2 agonists on presynaptic C fibres while augmentation of motor effects may be due to hyperpolarization of motor neurons in dorsal horn by $\alpha_2$agonists.[5,7,12] Intrathecal dexmedetomidine has been used in various animals in doses ranging from 2.5 to 100 µg without any signs of neurotoxicity.[13-19]

Kanazi et al studied effects of adding 3 µg dexmedetomidine to 12 mg hyperbaric bupivacaine and found that it prolonged duration of motor and sensory block and accelerated the onset of motor block without producing any significant adverse effects.[5] Gupta et al found that adding 5 µg dexmedetomidine to 3 ml of 0.75% isobaric ropivacaine in lower limb surgery retarded the regression of sensory block, increased the time to first analgesic request and reduced the postoperative analgesic requirements. However, the intraoperative ephedrine requirement for treatment of hypotension was significantly increased in the group receiving dexmedetomidine as compared to control.[8] Shukla et al reported that adding 10 µg dexmedetomidine to 15 mg bupivacaine prolonged the sensory and motor block times than patients not receiving any spinal adjuvant. They did not find any significant adverse effects.[4] Al Mustafa et al studied effects of adding 5 and 10 µg dexmedetomidine to 10 mg bupivacaine and concluded that there was dose dependent effect of dexmedetomidine on onset and regression of sensory and motor block.[20]Eid et al used 10 and 15µg dexmedetomidine as adjuvant to spinal bupivacaine and found that dexmedetomidine produced dose dependent prolongation in duration of sensory and motor block and time to 1st analgesic request and reduced postoperative analgesic requirements. Patients receiving 15 µg dexmedetomidine had higher sedation scores as compared to control group.[9]

In our study, we observed that adding dexmedetomidine to intrathecal ropivacaine resulted in dose dependent prolongation of duration of sensory and motor block up to 10 µg dexmedetomidine, after which increasing the dose to 15µg did not yield additional benefit. Similar findings were observed for time to 1st analgesic request, maximum VAS score and total postoperative analgesic requirements. Onset of sensory and motor block was quickened only after increasing the dose of dexmedetomidine to 5 µg and 10 µg respectively. For both parameters, onset times were not further reduced by 15 µg dexmedetomidine. Group receiving 15 µg dexmedetomidine had higher incidence of hypotension and bradycardia than the control group. Accordingly, the amount of ephedrine and atropine required was also significantly increased. The above findings suggest that dexmedetomidine in 10 µg dose potentiates the ropivacaine induced subarachnoid block without significantly increasing the adverse effects. Increasing the dose of dexmedetomidine to 15 µg does not add any additional benefit but increases the adverse effects.

Our study established that dexmedetomidine potentiates the sensory and motor characteristics subarachnoid block induced by isobaric ropivacaine in a dose dependent manner up to 10 µg, after which there is no improvement in block characteristics and adverse effects increase significantly. We conclude that dexmedetomidine in dose of 10 µg is preferable to other doses in terms of balance between potentiation of subarachnoid block and development of undesirable effects.

References:

1. Wiles MD, Nathanson MH. Local anaesthetics and adjuvants – future developments. Anaesthesia 2010;65:22–37.

2. Christiansson L. Update on adjuvants in regional anaesthesia. Period boil 2009;111:161-70.

3. Albrecht E, Kirkham KR, Liu SS, Brull R. The analgesic efficacy and safety of neuraxial magnesium sulphate: a quantitative review. Anaesthesia 2013;68:190–202.

4. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulphate used as adjuvants to bupivacaine. J Anaesthesiol Clin Pharmacol 2011;27:495–9.

5. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. ActaAnaesthesiolScand 2006;50:222-7.

6. Grewal A. Dexmedetomidine: New avenues. J Anaesthesiol Clin Pharmacol 2011;27:297–302.

7. 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;27:339-43.

8. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. Indian J Anaesth 2011;55:347-51.

9. Hala EA, Eid MD, Mohamed A, Shafie MD, Hend Youssef MD. Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine. Ain Shams J Anesthesiol 2011;4:83-95.

10. Eisenach JC, Shafer SL, Bucklin BA, Jackson C, Kallio A. Pharmacokinetics and pharmacodynamics of intraspinal dexmedetomidine in sheep. Anesthesiology 1994; 80: 1349–59.

11. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, et al. Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. Indian J Anaesth 2011;55:116-21.

12. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav1985 ;22:845-58

13. Lo WC, Harris J, Clarke RW. Endogenous opioids support the spinal inhibitory action of an alpha 2-adrenoceptor agonist in the decerebrated spinalised rabbit. Neurosci Lett 2003;340:95-8

14. Xu M, Kontinen VK, Kalso E. Effects of radolmidine, a novel alpha2-adrenergic agonist compared with dexmedetomidine in different pain models in the rat. Anesthesiology 2000;93:473-81.

15. Talke P, Xu M, Paloheimo M, Kalso E. Effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on EMG in rats. Acta Anaesthesiol Scand 2003;47:347-54.

16. Shimode N, Fukuoka T, Tanimoto M, Tashiro C, Tokunaga A, Noguchi K. The effects of dexmedetomidine and halothane on the Fos expression in the spinal dorsal horn using a rat postoperative pain model. NeurosciLett 2003;343:45-8.

17. Horvath G, Joo G, Dobos I, Klimscha W, Toth G, Benedek G. The synergistic antinociceptive interactions of endomorphin-1 with dexmedetomidine and/or S (+)-ketamine in rats.AnesthAnalg 2001;93:1018-24.

18. Onttonen T, Pertovaara A. The mechanical antihyperalgesic effect of intrathecally

administered MPV-2426, a novel alpha2-adrenoceptor agonist, in a rat model of postoperative pain. Anesthesiology 2000;92:1740-5.

19. Takano Y, Yaksh TL. Characterization of the pharmacology of intrathecally administered alpha 2-agonists and antagonists in rats. J PharmacolExpTher 1992;261:764-72

20. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, et al. Effect of Dexmedetomidine added to spinal bupivacaine for urological procedure. Saudi Med J 2009;30:365-70.