

International Journal of Medical Science and Current Research (IJMSCR) Available online at: www.ijmscr.com Volume3, Issue 3, Page No: 177-183 May-June 2020



Comparative Study of Small Dose Intrathecal Nalbuphine and Dexmedetomidine as Adjuvants in Abdominal Hysterectomy

¹Dr. Ritchie Edmund Pasweth, ²Dr. Takhelmayum Hemjit Singh*, ³Dr. Nongthombam Ratan Singh, ⁴Dr. Adrish Banik, ⁵Dr. Vasantharajan V, ⁶Dr. Malin Debnath ^{1,4,5,6}PGT, ²Associate Professor, ³Professor

Department of anaesthesiology, RIMS, Imphal, India

*Corresponding Author: Dr. Takhelmayum Hemjit Singh

Associate Professor, Department of anaesthesiology, RIMS, Imphal, India

Type of Publication: Original Research Paper Conflicts of Interest: Nil

ABSTRACT

Background

Neuraxial adjuvant have been used to enhance the effect of spinal anaesthesia and recently the role of intrathecal nalbuphine and dexmedetomidine as a promising adjuvant have been highlighted in some studies. Hence, the present study was designed to compare the block characteristics and secondary effect of small dose intrathecal nalbuphine (0.4 mg) and dexmedetomidine (5µg) in abdominal hysterectomy under subarachnoid block.

Methods

The study was a randomized, comparative, double-blinded one conducted in a tertiary care centre at Imphal, Manipur for a duration of two years in which sixty adult female patients of ASA I &II, aged between 18-60 years undergoing abdominal hysterectomy under spinal anaesthesia were randomized into two groups viz: Group N- received 2.5 ml. 0.5% hyperbaric bupivacaine + 0.5 ml (0.4mg) Nalbuphine and Group D- received 2.5ml. 0.5% hyperbaric bupivacaine + 0.5ml(5µgm) Dexmedetomidine. The haemodynamics parameters, time of analgesia at T₁₀ dermatome, onset of sensory block, duration to achieve maximum sensory level, duration to first rescue analgesic request, sedation score, side effects were recorded and compared between the two groups. Results

The demographic parameters were comparable in the two groups. Group D recorded significant longer rescue analgesic free time interval as compared with group N(290.16±35.32 Vs 240.36±28.21 minutes). The onset of sensory block was shorter in group D and statistically significant(25.20±5.82 secs Vs 30.35±7.535 secs, P=0.005). The haemodynamics variable were comparable in the two groups (P>0.05). None of the patients in the two groups were sedated with any side effects. Conclusion

Intrathecal dexmedetomidine as adjuvants to hyperbaric bupivacaine in spinal anaesthesia seems to be a better alternative to intrathecal nalbuphine as it provides early onset of sensory block, prolonged duration of sensory and motor block with adequate postoperative analgesia without significant haemodynamic alterations and side effects

Keywords: Dexmedetomidine, Intrathecal adjuvants, Nalbuphine, Small dose

INTRODUCTION

Pain is a protective mechanism and occurs whenever any tissues are being damaged and it causes the individual to act to remove the pain stimulus. It is an extraordinary complex sensation which is difficult to define and equally difficult to measure in an accurate and objective manner.^[1]

Spinal anesthesia is a commonly used technique for lower abdominal and lower limbs surgeries. It has several advantages like ease of administration, rapid onset of action, good muscle relaxation and early recovery.^[2] However, post operative pain control is a major problem with this technique, as the use of only local anaesthetic is associated with relatively short duration of action, requiring early analgesic intervention in the early post operative period.^[3]

Some of the neuraxial adjuvant that have been used to enhance the effect of spinal anaesthesia include (morphine, fentanyl, nalbuphine, opioids and buprenorphine), sodium bicarbonate (NaHCO3), vasoconstrictors (epinephrine), alpha-2 adrenoceptor (clonidine and dexmedetomidine), agonists cholinergic agonists, N-methyl-d-aspartate (NMDA) antagonists (ketamine) and γ -aminobutyric acid (GABA) receptor agonists (midazolam).^[4]

Nalbuphine, a μ antagonist and κ agonist, is a potent analgesic with analgesic potency almost equivalent to that of morphine on a milligram basis based on relative potency studies using intramuscular administration.^[5] The addition of 0.4 mg of nalbuphine to hyperbaric tetracaine improved the quality of intra and postoperative analgesia.^[6] On the other hand, Dexmedetomidine is a relatively new highly selective $\alpha 2$ agonist with analgesia, sedation, anxiolysis, and sympatholysis as its useful pharmacological actions.^[7] Dexmedetomidine was suggested as an additive to local anaesthetics in peripheral and neuraxial blocks.^[8,9]

However, only a few workers have conducted studies comparing the effects of small dose intrathecal nalbuphine and dexmedetomidine as adjuvants. A study by Kurhekar et al^[10] found the effect of intrathecal 2.5 μ g dexmedetomidine comparable to 250 μ g morphine in gynaecological studies, while Gupta R et al^[3] found the optimal dose of intrathecal dexmedetomidine to be 5 μ g for satisfactory analgesia with minimal side effects. Hence, the present study was designed to compare the block characteristics and secondary effect of small dose intrathecal nalbuphine (0.4 mg) and dexmedetomidine (5 μ g) in abdominal hysterectomy under subarachnoid block.

Materials and methods

The study was a randomized, comparative, doubleblinded one conducted in a tertiary care centre at Imphal, Manipur for a duration of two years period starting from September 2017 to August 2019 in which sixty adult female patients of ASA I &II, aged 18-60 years undergoing between abdominal hysterectomy under spinal anaesthesia were recruited for the study after taking approval from the Institute Ethics Committee and written informed consent from the patient. Patient with history of allergy to the study drugs, bleeding tendency, local site infection, uncooperative, cardiac, respiratory and kidney

diseases, patients with neurological deficit and spinal deformity were excluded from the study.

A computer generated randomization chart was used and a particular patient was assigned to one of the two groups depending on the randomization chart viz: Group N- received 2.5 ml. 0.5% hyperbaric bupivacaine + 0.5 ml (0.4mg) Nalbuphine and Group D- received 2.5ml. 0.5% hyperbaric bupivacaine + 0.5ml(5µgm) Dexmedetomidine. An uniform anaesthetic technique were maintained for all the enrolled patients. Patients were premedicated with tablet alprazolam 0.5mg night before the surgery after a thorough preoperative assessment. Injection ranitidine 50 mg and injection metclopramide 10 mg was given in the morning of surgery before the operative procedure. On arrival at the operation theatre monitoring of heart rate (HR), non invasive blood pressure (NIBP), oxygen saturation (SPO₂) and electro- cardiogram (ECG) were started. All the patients received intravenous ringers lactate solution 10 ml per kg as preloading solution within 30 minutes of subarachnoid block.

Dural puncture was performed in L_2 - L_3 interspace under strict sterile conditions using a 25 G Quincke needle in the left lateral position by an anesthetist who was not known to the study drugs. After confirming the dural puncture with free flow of cerebrospinal fluid, spinal anesthesia was performed with 2.5 ml of 0.5% hyperbaric bupivacaine with either of the two adjuvants, depending on the group.

Hypotension defined as fall in the systolic blood pressure (SBP) more than 20% of the baseline blood pressure or less than 100 mm Hg was treated with fluids(100 ml of Ringers Lactate) or with intravenous mephentermine in increments of 3 mg as an when required. Bradycardia (heart rate [HR] <50 bpm) was treated with injection atropine 0.3–0.6 mg intravenously. Time of analgesia at T_{10} dermatome i.e time interval from the local anaesthetic drug administration and the onset of cutaneous analgesia at T_{10} was assessed using a midline bilateral pinprick every minute, till complete loss of cutaneous sensation at T_{6} - T_{8} , at which point the surgical procedure was commenced / proceeded. Maximum analgesic dermatome achieved and its duration were assessed and noted. The degree of motor block was assessed when the cutaneous sensation is lost at T_{10} .¹¹ Time to two segment regression and sensory

Volume 3, Issue 3; May-June 2020; Page No.177-183 © 2020 IJMSCR. All Rights Reserved regression to S_2 were also recorded. Sedation score was recorded just before the initiation of surgery and then every 30 minute till the end of surgery.^[12] Also, the duration of analgesia was recorded as the time interval from the time of intrathecal drug injection till the time when the patient first complains of pain i.e. the first demand for rescue analgesia or VAS (Virtual analogue scale)^[13]>4 and then rescue analgesia was provided by intramuscular injection of diclofenac 75 mg. The details of any other adverse effects (if any) was recorded, noted and compared.

Sample size was calculated based on the previous study of Mukherjee A et al^[9] for an α value of 0.05 and β value of 0.2(power(1- β)= 80%), where we recruited 30 patients for each group. All the patients fulfilling the inclusion criteria coming within this data collection period were included. The data summarised collected were using descriptive statistics like percentage, mean, etc. **Statistical** analysis of the data obtained were done using Windows based Statistical Package for Social Sciences [SPSS] Version 21.0 (Armonk, NY:IBM Corp) by using independent Students t test for continuous data, Chi square test for categorical data, etc, whichever were appropriate and P<0.05 was considered as statistically significant.

Results and observation

The study protocol were completed in all the enrolled patients. The demographic parameters such as age, weight, height and ASA in the two groups were comparable (P>0.05) and did not affect the study outcome, as shown in table 1.

Table1:	Distribution	and	comparison	of
demogra	phic parameters	in the	two groups.	

S l n o	Parame ters	Group N (n=30)	Group D (n=30)	Statist ical test value	P- val ue
1	Age in years (Mean ±SD)	45.90 ±6.445	46.50 ±7.011	't" test value of 0.345	0.7 31
2	Weight in Kgs (Mean	60.53 ±5.008	60.23 ±6.285	't" test value of	0.8 39

		-			
	$\pm SD$)			0.204	
3	Height in Cms (Mean ±SD)	161.200 ±5.733	161.900 ±6.586	't" test value of 2.868	0.6 90
4	ASA (I:II)	24:6	22:8	Chi square value of 0.09	0.7 6

The mean onset of sensory block was achieved earlier in group D as compared with group N and the difference was statistically significant, as shown in table 2. Also, the duration to achieve the maximum T_{10} sensory level was faster in group D and statistically significant as compared with group N. However, the time to achieve the maximum sensory level was comparable and statistically not significant in both the groups. Again, the duration for two segment dermatome regression was longer in group D and statistically highly significant when compared with group N. Group D recorded significant longer rescue analgesic free time interval as compared with group N(290.16±35.32 Vs 240.36±28.21 minutes).

Table 2: Distribution and comparison ofstudyoutcome characteristics in the two groups

S l n o	Study outco me variabl e	GroupN(n =30) Mean±S D	GroupD(n =30) Mean±S D	Indepen dent 't' test value	P- valu e
1	Onset of sensory block in second s	30.35 ± 7.535	25.20 ± 5.824	2.952	0.00 5*
2	Durati on to achieve T_{10} sensory level(m in)	1.68±0.54 6	1.43±0.32 1	2.164	0.03 5*

2	Durant	679	6.62	0.571	0.57
5	Durati	0./8	0.62	0.571	0.57
	on to	± 0.73	<u>+</u> 1.29		0
	achieve				
	maxim				
	ит				
	sensory				
	level				
	(minute				
	s)				
1	Durati	100.83+0	130 53 + 2	1 957	0.00
4	on for	109.63 <u>1</u> 9.	130.33 ± 2	4.937	0.00
	on jor	94	0.39		0.
	two				
	segmen				
	t				
	dermat				
	ome				
	regress				
	ion in				
	minutes				
5	Durati	240.36	291.16+3	6.155	0.00
-	on to	+2821	5 32		0*
	first		5.52		Ŭ
	rescue				
	analoes				
	in				
	raquast				
	request				

*= Significant

The hemodynamic variables such as systolic and diastolic blood pressure, heart rate and peripheral oxygen saturation at different time points were comparable in the two groups (P>0.05). The side effects such as bradycardia, nausea, vomiting, pruritis, respiratory depression and sedation were absent in the two groups during the study period. However, two patients in each groups recorded intraoperative hypotension which were managed with inj. mephenteramine and was usually an associated finding of spinal anaesthesia.

Discussion

Spinal anesthesia is the most commonly used technique chosen for lower abdominal and lower limb surgeries owing to its simplicity, rapid onset and avoidance of airway manipulations. Although neuraxial anesthesia has many advantages over general anesthesia, limited duration of action is one of the most important disadvantages when spinal ansesthesia is used alone, requiring early analgesic

intervention in the postoperative period. A number of adjuvants to local anesthetics such as opiods, alpha2 adrenoceptors have been studied to prolong the effect of spinal anesthesia.^[2]

Opiods have been used sucessfully for years as adjuvants to local anesthetics but its use is limited by its side effects like nausea, vomiting, pruritus, urinary retention and respiratory depression.^[14] Nowadays, newer drugs like clonidine and dexmedetomidine which are alpha2 agonist has gained tremendous popularity and is replacing opiods as is devoid of unwanted side effects.^[2,3,7,10] opiods induced Similarly. lot of studies has been done on intrathecal nalbuphine by various authors^[14,15,16,17] and concluded 0.4mg as the most ideal dose. Therefore in our study we were comparing the efficacy of nalbuphine (0.4mg) and dexmedetomidine (5µg) as adjuvants in abdominal hysterectomy under spinal anesthesia using bupivacaine as the local anesthetic.

The sensory onset time, in our study, was faster in group D as compared to group N(P<0.05). Also, the mean onset time of sensory block at T₁₀ in group D was faster than group N and the difference was statistically significant. These results were comparable with the study of Kanazi et al^[18]. Similar results were also recorded with the study of Michael RM and Mehta M et al^[3] where the onset of sensory blockade was significantly earlier in group D than group N (p<0.00). In our study, the mean time taken to reach maximum sensory block level and time for complete motor blockade was not statistically significant (P=0.570,0.785) which is consistent with the study done by Prabhakariah et al^[19] where nalbuphine 0.8mg and fentanyl 25µg as an adjuvants intrathecal 0.5% bupivacaine 12.5mg were to compared for postoperative analgesia and adverse effects, and they recorded the time to achieve maximum sensory block was not significant(p=0.225). These findings were also in concordance with the results of Al Ghanem et al^[20] who observed no difference in the onset time in patients receiving dexmedetomidine (7.5 \pm 7.4 min) and fentanyl (7.4 \pm 3.3 min) as adjuvants to isobaric bupivacaine (P =0.95). The onset time observed in the study conducted by Al Ghanem et al^[20] were relatively longer than those observed by us which can be attributed to their use of isobaric bupivacaine, difference in definition of onset time (T_{10} dermatome vs T_8 in our study) and area of lumbar puncture.

Volume 3, Issue 3; May-June 2020; Page No.177-183 © 2020 IJMSCR. All Rights Reserved

We observed in our present study that the time to two segment dermatome regression of sensory block was significantly prolonged in group D (130± 20.59 min) as compared to group N (109.83±9.94 min)(P=0.000). The mean time to sensory regression at S_2 was 220.39±47.7 minutes in group N and 276.6±49.01 minutes in group D and also found to be highly statistically significant(P=0.000). These results were found to be in agreement with the study of Gupta R et al^[3] who evaluated onset and duration of sensory and motor block of dexmedetomidine and fenatanyl and concluded that group D had a significantly longer sensory and motor block time than group F. The mean time of sensory regression to S_1 was 476±23 min in group D and 187 ± 12 min in group F (P<0.001). The regression time of motor block to reach modified Bromage 0 was 421±21 min in group D and 149±18 min in group F (P<0.001). This is also supported by Kanazi et al^[18] who showed that the combination of 12 intrathecal bupivacaine mg of with dexmedetomidine significantly prolonged the mean duration of sensory and motor block, in comparison with bupivacaine alone(p < 0.001). The prolongation of sensory and motor block in our study could be attributed to the difference in the mechanism of action of dexmedetomidine and nalbuphine.

In our study, both dexmedetomidine and nalbuphine provided good quality intraoperative analgesia and haemodynamic stability. However, the duration of postoperative analgesia (from intrathecal injection to first rescue analgesic when VAS>3) was significantly prolonged in group D (291.16± 35.32 min) as compared to group N (240.36± 28.21 min). Similarly, Michael RM and Mehta M et al^[2] compared intrathecal nalbuphine and dexmedetomidine and found that the duration of analgesia was prolonged in group D (276.07±31.28 minutes) as compared to group N (200.67±22.18 minutes) which is consistent with our findings. Also, significant analgesic efficacy was seen by Gupta R et al^[3] on comparison of dexmedetomidine (251.7±30.69 min) and fenatanyl (168.96±15.96 min). Al-Mustafa et al^[21] observed dose dependent prolongation of motor and sensory blockade with reduced analgesic requirement with increasing dosages of intrathecal dexmedetomidine (5µg and 10µg). Al-Ghanem SM et al^[20] had studied the effect of addition of $5 \mu g$ dexmedetomidine or $25 \mu g$ fentanyl intrathecal to 10 mg isobaric bupivacaine in

vaginal hysterectomy and concluded that $5 \mu g$ dexmedetomidine produces more prolonged motor and sensory block as compared with 25 µg fentanyl.

The mechanisms by which intrathecal dexmedetomidine prolong the motor and sensory block of local anesthetics is not well understood. Intrathecal alpha 2-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons, and the prolongation of motor block may be the results of synergistic effect of local anesthetics and alpha 2 agonist or its binding on motor neuron on dorsal horn.^[2,3,7,22] Nalbuphine, with mixed µ antagonist and k agonist properties, provided potent analgesia in certain models of visceral nociception due to its action on kappa receptors.^[14,15,16]

The overall haemodynamic profile of both the groups was almost similar and statisacally insignificant. These findings were consistent with that reported by Kanazi et al^[18], Al-Ghanem et al^[20], Michael RM and Mehta M et al^[2] who also found less haemodynamic changes. Peripheral oxygen saturation at different time intervals were comparable in the two groups and side effects like nausea/vomiting, bradycardia, pruritus, respiratory depression and sedation was not seen in both the groups, and the same results were also reported in the study by Mukherjee A et al.^[15]

The results obtained in our present study were similar with the various studies^[2,3,18,20] demonstrating that dexmedetomidine $5\mu g$ was superior to nalbuphine 0.4mg in terms of faster onset of sensory block, prolongation of sensory and motor block and duration of postoperative analgesia without significant hemodynamic changes.

Our study was not without any limitation. Different doses of the two study drugs and in different ASA classification needs to be evaluated. Future research will be appropriate to determine dose-related response to nalbuphine and its potential to reduce local anesthetic dose in intravenous and neuraxial route.

Conclusion

Intrathecal dexmedetomidine 5µg supplementation as adjuvants to hyperbaric bupivacaine in spinal anaesthesia seems to be a better alternative to intrathecal nalbuphine 0.4mg as it provides early onset of sensory block, prolonged duration of sensory

Dr. Takhelmayum Hemjit Singh *et al* International Journal of Medical Science and Current Research (IJMSCR)

and motor block with adequate post-operative analgesia without significant haemodynamic alterations and side effects. So, intrathecal dexmedetomidine is a better adjuvant compared to intrathecal nalbuphine for patients undergoing abdominal hysterectomy.

References

- Guyton AC, Hall JE. Somatic sensations, pain, headache and thermal sensations. In: Guyton AC, Hall JE, editors. Textbook of Medical Physiology. 11th ed. Philadelphia, Pa: Saunders/Elsevier; 2006.p.598-605.
- Michael RM, Mehta M. Comparison between dexmedetomidine and nalbuphine as an adjuvant to bupivacaine in spinal anesthesia. Int J Adv Res 2016; 3(1):1024-45.
- 3. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl adjuvants to Bupivacaine. J Anaesth Clin Pharmacol 2011;27(3):339-43.
- 4. Anderson CTM. Adjuvants in Regional and Neuraxial Anesthesia: An Update.2013;[12screens].Availableat:URL:htt p://www2.Pedsanesthesia.org/meetings/2013 winter/syllabus/submissions/sig-pain/CAnder son.pdf. Accessed July 16, 2017.
- 5. Beaver WT, Feise GA. A comparison of the analgesic effect of intramuscular nalbuphine and morphine in patients with postoperative pain. J Pharmacol Exp Ther 1978;204(2):487-96.
- Lin ML. The analgesic effect of subarachnoid administration of tetracaine combined with low dose of morphine or nalbuphine for spinal anaesthesia. Ma TsuiHsuehTsa Chi 1992;30:101-5.
- Gupta M, Gupta P, Singh DK. Effect of 3 different doses of intrathecal dexmedetomidine (2.5µg, 5µg, and 10 µg) on subarachnoid block characteristics: A prospective randomized double blind doseresponse trial. Pain Physician 2016 Mar; 19:E411-20.
- 8. Agarwal S, Aggarwal R, Gupta P. Dexmedetomidine prolongs the effect of

bupivacaine in supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol 2014;30(1):36–40.

- Esmaoglu A, Mizrak A, Akin A, Turk Y, Boyaci A. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. Eur J Anaesthesiol 2005;22(6):447–51.
- 10. Kurhekar P, Kumar SM, Sampath D. Comparative evaluation of intrathecal morphine and intrathecal dexmedetomidine in patients undergoing gynaecological surgeries under spinal anaesthesia: A prospective randomised double blind study. Indian J Anaesth 2016 Jul;60(6):382-7.
- Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand Suppl 1965;16:55-69
- 12. Gupta R, Kaur S, Singh S, Aujla KS. A comparison of epidural butorphanol and tramadol for postoperative analgesia using CSEA technique. J Anaesthesiol Clin Pharmacol 2011;27(1): 35–8.
- 13. Revar B, Patel V, Patel B, Padavi S. A comparison of epidural butorphanol tartarate and tramadol hydrochloride for post operative analgesia using CSEA technique. Int. J Res Med 2015;4(1):1-6.
- 14. Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecal nalbuphine compared with intrathecal morphine after cesarean delivery: an evaluation of postoperative analgesia and adverse effects.AnesthAnalg 2000 Sep;91(3):601-5.
- 15. Mukherjee A, Pal A, Agrawal J, Mehrotra A, and Dawar N. Intrathecal nalbuphine as an adjuvant to subarachnoid block: What is the most effective dose? Anesth Essays Res 2011 Jul-Dec;5(2):171-5.
- 16. Moustafa MA, Saleh RS. Nalbuphine added to intrathecal morphine in total knee arthroplasty; effect on postoperative analgesic requirements and morphine related side effects. Alex J Med 2012 Mar;48:175-8.

Dr. Takhelmayum Hemjit Singh *et al* International Journal of Medical Science and Current Research (IJMSCR)

- 17. Jyothi B, Gowda S, Shaikh SI. A comparison of analgesic effect of different doses of intrathecal nalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal and orthopedic surgeries. Indian J Pain 2014 Jan-Apr;28(1):18-23.
- 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. Acta Anaesthesiol Scand. 2006;50:222-7.
- 19. Prabhakaraiah UN. Naravanappa AB. Gurulingaswamy Kempegowda S. K. Vijaynagar KA, Hanumantharayappa NB, et al. Comparison of nalbuphine hydrochloride and fentanyl as an adjuvant to bupivacaine for spinal anesthesia in lower abdominal

surgeries: A randomized double-blind study. Anesth Essays Res 2017;11:859-63.

- 20. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, et al. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynaecological procedures: A double blind controlled study. American journal of applied sciences 2009;6(5):882-7.
- 21. 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 procedures. Saudi Med Journal 2009 Mar;30(3):365-70.
- 22. Eisanach JC, De Kock M, Klimscha W. a2 adrenergic agonists for regional anesthesia. Anesthesiology 1996; 85: 655—74.