ORIGINAL ARTICLE

Comparison of different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing caesarian section

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ABSTRACT

Background: The necessity to find out the lowest possible effective dose of clonidine to avoid its known side effects like hypotension, bradycardia and sedation prompted us to design present study. We compared different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia in patients undergoing caesarian section aiming to find out the lowest possible effective dose.

Methods: In a prospective, double-blind, randomized controlled study, 60 parturients 18 to 35 years of age, ASA grade I or II, posted for caesarian section were randomly distributed into three equal groups, BC60, BC30 and BC15. Patients were given 2.0 ml of hyperbaric bupivacaine 0.5% with 60 μg, 30 μg or 15 μg of clonidine intrathecally respectively. Hemodynamic parameters, onset, peak and duration of sensory and motor block, level of sedation and duration of postoperative analgesia were compared.

Results: All groups were comparable with respect to demographic profile, onset, peak and duration of sensory and motor block and overall hemodynamic stability. We observed dose dependent variability in duration of analgesia and sedation. Duration of analgesia was significantly higher in BC60 group as compared to the other two groups (598.7 $\pm$ 140.47 vs. 436.65 $\pm$ 149.84 and 387.1 $\pm$ 97.05 minutes respectively). Sedation was also more in BC 60 group.

Conclusion: Addition of 60 μg clonidine to intrathecal bupivacaine provides longer duration of postoperative analgesia than 15 μg or 30μg but with more sedation. We get fairly good analgesia with less sedation in 15μg and 30μg clonidine and are better options when sedation is not desirable.

Key words: Intrathecal; Clonidine; Bupivacaine; Postoperative analgesia; Spinal anesthesia

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INTRODUCTION

Spinal anesthesia has increasingly become the technique of choice for lower segment caesarian section.[1] It has the advantages of simplicity of technique,[2,3] rapid onset of action and reliability in producing uniform sensory and motor blockade as compared to epidural anesthesia.[4-6] Its main disadvantage relates to its limited duration of action and hence lack of long-lasting postoperative analgesia. Spinal anesthesia and postoperative analgesia can be prolonged by using adjuvant to local anesthetic like adrenaline,[7] midazolam,[8] opioids, neostigmine, clonidine, etc.[9-14] Clinical studies have suggested that intrathecal clonidine prolongs sensory as well as motor block of spinal anesthesia. It decreases local

anesthetic requirements and provides prolonged postoperative analgesia.[9,14-17] Other beneficial effects are antiemesis, reduced post spinal shivering, anxiolysis and sedation.[18] At the same time it causes bradycardia and hypotension that may have deleterious effects on fetus when administered for Cesarean section. Increased sedation caused by it may also be unwanted at times. The necessity to find out the lower effective dose of clonidine to avoid its known side effects like hypotension and bradycardia and sedation prompted us to design present study.

In this study, we have compared three different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia in patients undergoing caesarian section aiming to find out the lowest possible effective dose among them. Primary outcome measure compared was duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. Secondary outcome measures compared were demographic characteristics, onset peak and duration of sensory and motor blockade, level of sedation, maternal hemodynamic parameters and fetal parameters.

METHODOLOGY

A prospective, double-blind, randomized, controlled study design with three parallel groups was planned. After prior approval from institutional ethics committee, study was conducted at Pravara Institute of Medical Sciences, Loni (India) during the period from August 2010 to November 2011, on 60 parturients of age group between 18–35 years, ASA grade I or II and posted for lower segment caesarian section. Informed written consent was obtained from all the parturients. Exclusion criteria were complicated pregnancy including pregnancy induced hypertension, placenta previa, abruptio placenta; severe systemic disorder including diabetes mellitus, hypertension, heart disease changing ASA grading to more than II; allergy to bupivacaine or Clonidine and all known contraindications for spinal anaesthesia, such as spine deformity, increased intracranial pressure, neurological disorders, hemorrhagic diathesis, or infection at the puncture site. Parturients were randomly distributed into three groups of 20 patients each & randomization was concealed.

Group BC60 (n=20)

In this group, each patient was given 2.0 milliliters (ml.) of hyperbaric bupivacaine 0.5% (10 milligrams [mg]) with 15 micrograms (μg) of clonidine, intrathecally.

Group BC30 (n=20)

In this group, each patient was given 2.0 ml of hyperbaric bupivacaine 0.5% (10mg) with 30μg of clonidine, intrathecally.

Group BC15 (n=20)

In this group, each patient was given 2.0 ml of hyperbaric bupivacaine 0.5% with 60μg of clonidine, intrathecally.

Method of randomization was blocked randomization. Randomization was carried out based on blocking. Blocks of size 3 with treatment allocation of 1: 1: 1 for group BC15, group BC30, group BC60 were created. A block of 3 patients was assigned to one of the blocks created, leading to random assignment of one subject to one group.

The sample size could not be calculated before the start of the study due to paucity of similar studies. Post-hoc power analysis was carried out for duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. This study had 94.16 % power to detect effect size of 162.05 minutes between group I and group II and power of 99.98 % to detect effect size of 211.6 minutes between group I and group III assuming alpha error 0.0500 (two-sided).

Sedatives and hypnotics were avoided in premedication as well as intraoperatively. All these patients were premedicated with antiemetic agent – inj. ondansetron (4 mg intravenously [i.v.]). Patients were preloaded with Ringer Lactate (R.L.) 10-15 ml/kg. Pre-operative parameters like pulse rate, oxygen saturation and blood pressure were noted. Spinal anesthesia was given with 25G Quincke's needle in sitting position under all aseptic precautions. Depending upon the groups, respective agents were injected intrathecally. Group BC60 was given 2 ml of hyperbaric bupivacaine 0.5% with 60 μg clonidine intrathecally; BC30 was given 2 ml of hyperbaric bupivacaine 0.5% with 30 μg clonidine intrathecally; Group BC15 was given 2 ml of hyperbaric bupivacaine 0.5% with 15 μg clonidine intrathecally. Each group had a total volume of 2.5 ml made by addition of normal saline. Both the patient and anesthesiologist were blinded to the study solutions. Syringes were prepared just before the spinal injection ensuring the volumes of 2.5 ml by third person knowing the code to blind the anesthesiologist administering the drug and later on making the observations. Pulse and blood pressure were measured every 5 minutes for first 30 minutes and thereafter every 10 minutes. Number of occasions for pulse rate and blood pressure variations more than 20 % of baseline were noted in all groups. Bradycardia was treated with Inj. Atropine if persisted for longer time and was symptomatic.

Sensory block was tested by pinprick method. Degree of motor blockade was assessed by modified Bromage

scale (Table 1).

Table 1: Modified Bromage score as used by Breen et al. [19]

Score	Criteria
1	Complete block (unable to move feet or knee)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knee)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Following observations were made:

T_0 = Time of spinal anaesthesia

T_1 = Time of onset of sensory block

T_2 = Time of onset of motor block

T_3 = Time of peak sensory block

T_4 = Time to two segment regression of sensory level

T_5 = Time of wearing off of motor block

T_6 = Time to first dose of post-operative rescue analgesia

Baby Apgar score was monitored at 1, 5, and 10 minutes.

In the intraoperative period, patient was closely monitored for pulse rate, SpO_2, blood pressure and blood loss. Inj oxytocin 10U was added to R.L. after delivery of anterior shoulder. Any side effects such as nausea, vomiting, pain, shivering, pruritus, sedation, hypotension, bradycardia and respiratory discomfort were noted and treated with appropriate drugs if required.

Patients were assessed for degree of sedation & scoring was done as follows (Table 2);

Table 2: Campbell Sedation Score [20]

Score	Criteria
1	Wide awake
2	Awake and comfortable
3	Drowsy and difficult to arouse
4	Not arousable

Residual sensory blockade was monitored and its wearing off time was noted (when sensation to pin-prick regresses by 2 dermatomal segments). Residual motor blockade was monitored and its wearing off time was noted when patient started to lift legs against gravity. Patients were inquired frequently for degree of pain they felt with the help of visual analogue scale (VAS). VAS involves use of a 10cm line on a piece of white paper and it represents patient's opinion of degree of pain. It was explained to all patients preoperatively that one end of the line i.e. '0' marks "no pain" at all, while other end i.e. '10' represents "worst pain" she ever felt. Patient was asked to rate the degree of pain by making a mark on the scale. Thus the pain score was obtained by measuring the distance from the '0' end to the indicated mark. Post operative rescue analgesia (Inj. Diclofenac 75 mg intramuscular) was given when patient's VAS score reached > 4 and the time of injection of first analgesic drug was noted. This was taken as the time of wearing off analgesia.

Statistical analysis was carried out with Stata 10. Demographic characteristics, hemodynamic parameters, onset, peak and duration of sensory and motor block and duration of postoperative analgesia, level of sedation and foetal parameters were compared between groups and data was analyzed statistically. The association between explanatory variables and response variables were found out by simple linear regression analysis. For categorical data chi-square test was applied. $P < 0.05$ was considered significant. For clarity, a proportion of the results are expressed as a percentage but statistical calculations were performed on actual numbers.

RESULTS

Table 3 compares demographic profile among all groups. All groups were comparable with respect to their demographic profile. There was no significant difference in age, ASA status, height, weight, parity, duration of pregnancy and duration of labour between the groups ($p > 0.05$). All groups were also comparable with respect to their baseline hemodynamic parameters like baseline pulse rate (92.7 ± 12.80: 86.55 ± 10.10: 89 ± 12.08); baseline systolic blood pressure (121.3 ± 6.81: 115.15 ± 9.10: 119.85 ± 7.09); baseline diastolic blood pressure (77.45 ± 9.70: 73.80 ± 10.71: 77.55 ± 8.09) ($p > 0.05$). Patient from all groups were comparable with hemodynamic stability as shown in Table 4. No significant difference was found in average pulse rate (89.85 ± 15.20: 83.44 ± 9.92: 88.41 ± 13.60); average systolic blood pressure (108.71 ± 9.92:107.10 ± 12.22 :111.05 ± 10.26) and average diastolic blood pressure (62.3 ± 9.79: 60.63 ± 10.08: 63.25 ± 9.38) ($p > 0.05$) among different groups. No significant difference was found regarding pulse variation (18:15:29) and incidence of hypotension (17: 11: 17) in groups BC15, BC30, BC60 respectively ($p > 0.05$). Bradycardia less than 60 beats/ minute was observed in only five patients out of which

Table 3: Demographic characteristics (Mean ± SD)

Characteristics		BC60 Group (n =20)	BC30 Group (n =20)	BC15 Group (n =20)
Age in years		24.7±3.15	22.9±2.75*	23.4±3.50*
Height in cm		153.25±6.09	152.35±5.28*	152.8±5.71*
Weight in kg		59.65 ± 8.73	55.85±8.52*	59.5±9.42*
Duration of pregnancy in weeks		38.68±1.77	38.82±1.07*	38.74±1.59*
Duration of labour in hrs		4.55±4.01	2.9 ± 1.89*	3.35±2.23*
Parity	Primipara	6	6*	8*
	Secondpara	7	12*	10*
	Multipara	7	2*	2*

* p-value > 0.05 * * p-value significant at 0.05; * * * p-value significant at 0.01

Table 4: Comparison of Maternal Hemodynamic parameters (Mean ± SD)

Parameter	BC60 Group (n =20)	BC30 Group (n =20)	BC15 Group (n =20)
Baseline Pulse Rate per minute	89±12.08	86.55±10.10	92.7±12.80*
Baseline Systolic B.P. mm of Hg	119.85±7.09	115.15±9.10	121.3±6.81*
Baseline Diastolic B.P.mm of Hg	77.55±8.09	73.8±10.71	77.45±9.70*
Average Pulse Rate per minute	88.41 ± 13.60	83.44±9.92	89.85±15.20*
Average Systolic B.P. mm of Hg	111.05± 10.26	107.10±12.22	108.71±9.92*
Average Diastolic B.P.mm of Hg	63.25±9.38	60.63±10.08	62.30±9.79*
Number of occasions of Bradycardia < 80 % of Base line	12	13	9*
Number of occasions of Tachycardia >120 % of Base line	16	4	9*
Number of occasions of fall in BP< 80 % of Base line	17	11	17*
Number of occasions of rise in BP > 120 % of Base line	0	1	0*

* p-value > 0.05 * *p-value significant at 0.05

two belonged to BC 60 group, two belonged to BC 30 group and only one belonged to BC 15 group. In one patient of BC 60 group pulse rate dropped up to the level of 50 beats/minutes needing intervention.

Table 5 compares onset, peak and duration of sensory and motor block and duration of postoperative analgesia. We could not appreciate any dose dependent variation in onset of sensory block (0.90±0.29 min: 0.95±0.30 min: 0.91±0.17 min); onset of motor block (1.48 ± 0.71 min: 1.59 ±0.52 min:1.71 ± 0.51 min); onset of peak sensory block (7.52±1.21 min: 7.79±1.61 min :7.54±1.80 min); two segment regression of sensory block (127.85±12.93 min:137.05±10.97 min:135.2±12.45 min) and wearing of motor block (5±14.61 min:186.2±11.12 min:182.1±10.08 min) ($p > 0.05$). We could appreciate dose dependent variation in duration of analgesia. Duration of analgesia was significantly higher in BC30 group (436.65 ± 149.84 min) than in BC15 group (387.1 ± 97.05 min) and in BC60 group (598.7±140.47 min) than in BC30 group ($p < 0.01$). Sedation score 4 was observed in none of the patients from all groups as per shown in Table 6. More patients from group BC 60 showed sedation score of 3.

Table 5: Comparison of Sensory, Motor blockade and Duration of analgesia (Mean ± SD)

Parameter	BC60 Group (n =20)	BC30 Group (n =20)	BC15 Group (n =20)
Time in minutes for onset of sensory blockade	0.91 ± 0.17	0.95 ± 0.30	0.90 ± 0.30*
Time in minutes for onset of motor blockade	1.71 ± 0.51	1.59 ± 0.52	1.48 ± 0.71*
Time in minutes for peak of sensory blockade	7.54 ± 1.80	7.79 ± 1.61	7.52 ± 1.21*
Two segment regression time in minutes for sensory blockade	135.2 ± 12.45	137.05 ± 10.97	127.85 ± 12.93*
Time in minutes for wearing off of motor block	182.1 ± 10.08	186.2 ± 11.12	186.5 ± 14.61*
Time in minutes for first rescue analgesia	598.7 ± 140.47	436.65 ± 149.84	387.1 ± 97.05***

*p-value > 0.05 **p-value significant at 0.05; ***p-value significant at 0.01

Table 6: Number of patients having sedation score in each group [(n (%)]

Sedation Score	Group BC 60	Group BC 30	Group BC 15	Total
Wide awake	1(5)	1 (5)	5 (25)	7
Awake and comfortable	14 (70)	17 (85)	15 (75)	46
Drowsy and difficult to arouse	5 (25)	2 (10)	0	7
Not arousable	0	0	0	0

P < 0.05

Table 7: Comparison of fetal parameters (Mean± SD)

Characteristics	Group BC 60 (n =20)	Group BC 30 (n =20)	Group BC 15 (n =20)
APGAR Score at 1 minute	7.35 ± 0.49	7.4 ± 0.60	7.35 ± 0.59*
APGAR Score at 5 minute	8.35 ± 0.49	8.4 ± 0.50	8.45 ± 0.51*
APGAR Score at 10 minutes	9.4 ± 0.50	9.45 ± 0.51	9.45 ± 0.51*

*p-value > 0.05

Table 7 shows overall foetal wellbeing in all groups. APGAR Scores at one minute, 5 minutes and 10 minutes after birth were comparable in all groups.

DISCUSSION

In recent years, clonidine which is a selective partial agonist for -2 adrenoreceptor has been used to prolong spinal Anaesthesia. It is known to increase both sensory and motor block of local anaesthetics.[9,12,14] Clonidine activates a negative feedback mechanism through stimulation of receptors and subsequent decreased catecholamine release. It also modulates input at dorsal horn by increasing potassium conductance. Clonidine also has cholinergic effects and increases the amount of acetylcholine available for modulating analgesia. The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic -2 receptor in substantia geletinosa of spinal cord.[21,22] There are many studies in the literature on beneficial effects of addition of intrathecal clonidine to bupivacaine, with different authors using different doses (15 to 300 mcg) of clonidine with satisfactory outcome. Previous use of large doses of clonidine (3μg/kg)[23] has been replaced by smaller doses[9-14] to reduce complications such as bradycardia, hypotension and sedation. Some researchers added 75 μg of intrathecal clonidine to local anesthetic for post operative analgesia.[10,13,14] We thought in the direction of further reducing the dose of clonidine without compromising its efficacy. We found very few studies[9,24,25] that compared different dosage of clonidine as an adjuvant to local anesthetic agent for spinal anesthesia and most of them are related to nonobstetric surgeries[24,25]. Elia N et al[26] included in their systematic review data from 22 randomized trials (1,445 patients) testing a large variety of doses of clonidine (15 to 150 μg), added to intrathecal bupivacaine, mepivacaine, prilocaine, or tetracaine aiming to quantify beneficial and harmful effects of clonidine when used as an adjuvant to intrathecal local anesthetics for surgery. They concluded that "the optimal dose of clonidine, however, remains unknown." In this study we compared three different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia in patients undergoing caesarian section, aiming to find out the lowest possible effective dose among them. Primary outcome variable considered was duration of analgesia (time to first dose of post-operative rescue analgesia). A small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension, or sedation.[9,12,14] The overall hemodynamic stability observed in all groups throughout the surgical procedure in our study conforms to this. There were very few occasions when pulse rate and blood pressure had rise or fall beyond 20 % of base line and very rarely hypotension or bradycardia needed to be corrected by drug intervention. Bradycardia requiring treatment was observed only in one patient out of total five, who responded well to atropine. In rest four patients bradycardia was not symptomatic and got corrected on its own. There was no significant difference between three groups regarding this. This was similar to the findings of earlier studies in which researchers used 1 mcg/kg of intrathecal clonidine for nonobstetric surgeries had also very few incidences of hypotension and bradycardia requiring intervention.[9,10,14,16.17] Hypotension and bradycardia in spinal anesthesia are caused by multiple confounding factors such as type of surgery (Obstetric or others), dose of bupivacaine used

, level of sympathetic block, hydration status etc.[9,12] Kothari N et al[12] who used low doses of clonidine (50 μg) showed that incidence of both hypotension and bradycardia was more in bupivacaine group than in bupivacaine with clonidine group. There was no difference in incidence of bradycardia by addition of clonidine. This was because of reducing the dose of bupivacaine from 12.5 mg to 10 mg. Bajwa SJ et al,[9] who used 9 mg of bupivacaine also did not observe bradycardia by addition of clonidine even up to 45 μg. So we also might not have observed any significant difference regarding hypotension and bradycardia between three groups due to low doses of clonidine and bupivacaine used. We could not appreciate any dose dependent variation in onset, peak and duration of sensory and motor block. We could appreciate dose dependent variation in duration of analgesia and sedation. Duration of analgesia was significantly higher in BC30 group than in BC15 group and in BC60 group than in BC30 group.($p < 0.05$) This implies that clonidine prolongs the duration of postoperative analgesia which is higher with increasing dose. This dose dependent variability in duration of analgesia has also been agreed upon by Saxena H et al[24] and Strebel et al[25] in nonobstetric surgery and by Bajwa SJ et al [9] in caesarean section surgery. We observed similar dose dependent variability in sedation also. We observed more sedation scores in BC 60 group than in BC 30 than in BC15 group. ($p < 0.05$) Kothari N et al[12] also found 35 to 45 % patients drowsy by addition of 50 μg of clonidine to bupivacaine; but Bajwa SJ et al[9] did not find any sedation by addition of up to 45 μg of clonidine to bupivacaine. Thus the sedation with clonidine is dose dependent.

CONCLUSION

In conclusion, intrathecal addition of 60μg clonidine to bupivacaine gives longer duration of postoperative analgesia than 15 μg or 30μg of clonidine but with more sedation. We get fairly good analgesia with less sedation in 15μg and 30μg clonidine and are better options when sedation is not desirable. At the same time when some amount of sedation is acceptable or required, addition of 60μg of clonidine that gives excellent analgesia with negligible hemodynamic complications is a better choice.

REFERENCES

1. Hunt CO. Spinal anesthesia for obstetrics. International Anaesthesiology Clinics. 1989;27:26-30.
2. Lucy SJ, Naugler MA. Spinal anesthesia for caesarean section (letter). Can J Anaesth. 1991;38:940-1.
3. Morgan P. Spinal anesthesia in obstetrics. Can J Anaesth. 1995;42:1145-63.
4. Covino BG. Rationale for spinal anesthesia. International Anaesthesiology Clinics. 1989;27:8-12.
5. Carter J, Macarthur A. Spinal anesthesia for Caesarean section. Contemporary Anesthesia. 1994;4:11-15.
6. Hunt CO, Dutta S, Hauch M. Perioperative analgesia with subarachnoid fentanyl-bupivacaine. Anaesthesiology. 1987;67.
7. Racle JP, B.A., Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg. 1987;66:442–6.
8. Prakash S, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. Reg Anesth Pain Med. 2006 May-Jun;31(3):221-6.
9. Bajwa SJ, Bajwa SK, Kaur J, Singh A, Singh A, Parmar SS. Prevention of hypotension and prolongation of postoperative analgesia in emergency cesarean sections: A randomized study with intrathecal clonidine. Int J Crit Illn Inj Sci. 2012 ;2(2):63-9..
10. Benhamou D, Thorin D, Brichant JF, Dailland P, Milon D, Schneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesth Analg. 1998;87(3):609-13.
11. Roelants F. The use of neuraxial adjuvant drugs (neostigmine, clonidine) in obstetrics. Curr Opin Anaesthesiol. 2006;19(3):233-7.
12. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth. 2011;5(1):31-5.
13. Lavand'homme PM, Roelants F, Waterloos H, Collet V, De Kock MF. An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg. 2008;107(3):948-55.
14. van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: a randomized controlled trial. Br J Anaesth. 2006;97(3):365-70.
15. Bonnet F, Buisson VB, Francois Y, Catoire P, Saada M. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth. 1990;15(4):211–4.
16. Sethi BS, Mary Samuel, Deepak Sreevastava. Efficacy of Analgesic Effects of Low Dose Intrathecal Clonidine as Adjuvant to Bupivacaine. Indian J Anaesth. 2007;51(5):415-19.
17. Shah BB, Shidhaye RV, Divekar DS, Panditrao M, Panditrao MM, Suryawanshi C. Effect of addition of Clonidine to Bupivacaine used for patients undergoing spinal anesthesia: A randomized, double blind, controlled study. Sri Lankan Journal of Anaesthesiology. 2011;19(1):17-21.
18. Dobrydnjov I, Axelsson K, Samarütel J, Holmström B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. Acta Anaesthesiol Scand. 2002;46(7):806-14.
19. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg. 1993;77:919-24.
20. Campbell DC, Camann WR, Datta S. The addition of bupivacaine to intrathecal sufentanyl for labour analgesia. Anaesth Analg. 1995;81:305-9.
21. Brandt SA, Livingston A. Receptor changes in spinal cord of sheep associated with exposure to chronic pain. Pain. 1990;42:323-9.
22. Reddy SVR, Yaksh TL. Spinal noradrenergic terminal system mediates antinociception. Brain Res.1980;189:391-401.
23. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anaesthesiol Scand. 1994;38(7):724-8.
24. H. Saxena, S.K. Singh, S. Ghildiyal: Low Dose Intrathecal Clonidine With Bupivicain Improves Onset And Duration of Block With Haemodynamic Stability. The Internet Journal of Anesthesiology. 2010;23(1). DOI: 10.5580/17df
25. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: a dose-response study. Anesth Analg. 2004;99(4):1231-8.
26. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. Reg Anesth Pain Med. 2008;33(2):159-67.

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