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CLONIDINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE FOR SPINAL ANESTHESIA IN ELDERLY PATIENTS UNDERGOING INFRAUMBLICAL SURGERIES

Anaesthesiology

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ABSTRACT

Background: Use of adjuvant with small doses of local anesthetics is a preferred technique for spinal anesthesia for lower limb surgeries. This study tested the hypothesis that addition of small doses of clonidine augments the spinal block levels produced by hyperbaric bupivacaine in patients without affecting the side-effects.

Materials and Methods: This was a prospective, randomized, double-blind study. Above 60 years patients were allocated to three equal groups. Group C received 10 mg hyperbaric bupivacaine without clonidine while Group C_{15} and Group C_{30} received 15 µg and 30 µg clonidine with hyperbaric bupivacaine respectively for spinal anesthesia. Effect of clonidine on sensory block levels was the primary study outcome measure. Motor blockade and hemodynamic parameters were also studied.

Results: A significantly higher median block levels were achieved in Group C_{15} ($P < 0.05$) and Group C_{30} ($P < 0.05$) than Group C. Highest median sensory block level, the mean times for sensory regression to T_{12} level and motor block regression were statistically significant between Groups C_{15} and C and between Groups C_{30} and C. On comparison of fall in systolic blood pressure trends, there was no significant difference in the clonidine groups as compared with the control group.

Conclusions: In elderly patients, clonidine when used intrathecally in doses of 15 µg or 30 µg with bupivacaine, significantly potentiated the sensory block levels and duration of analgesia without affecting the trend of systolic blood pressure as compared to bupivacaine alone. Clonidine in doses of 30 µg however facilitated the ascent of sensory level block to unexpectedly higher dermatomes for a longer time.

KEYWORDS

Clonidine, elderly, spinal anesthesia

INTRODUCTION-

The size of the elderly population, which refers to people of more than 60 years of age as defined by United Nations, continues to increase.[1] Thus, more elderly patients are expected to undergo surgical interventions.[2] Spinal anesthesia is frequently used in these patients for a number of surgeries.

A variety of anatomical and physiological changes related to ageing contribute to altered nerve block characteristics following subarachnoid administration of local anesthetics in elderly patients.[3] With hyperbaric local anesthetic solutions, the maximal height of spinal analgesia achieved has been found to increase with age.[4,5] Ageing changes in the cardiovascular system may lead to a frequent incidence of systemic hypotension and bradycardia associated with spinal anesthesia than the young.[6]

Lower doses of local anesthetics along with an adjuvant are preferred for spinal anesthesia in elderly patients. Clonidine, a selective partial alpha 2 adrenergic agonist, when administered intrathecally in adults for unilateral spinal anesthesia in very small doses of less than 1 µg/kg, has shown contradicting results in extending the sensory and motor blockade effects of local anesthetics with low incidence of side-effects e.g., hypotension, sedation and bradycardia.[7,8] The efficacy and safety of low doses has not been extensively studied in elderly patients. This study tested the hypothesis that in elderly patients, addition of clonidine in small doses of 15 µg and 30 µg to intrathecal hyperbaric bupivacaine 9 mg would augment sensory blockade. Effect on hemodynamic parameters and other block characteristics including motor blockade were also studied.

METHOD-

This prospective, randomized, double-blind study was undertaken after approval by the Institutional Ethics Committee and written informed consent from each patient.

In this study, 60 elderly patients of age more than or equal to 60 years, of American Society of Anesthesiologists (ASA) physical status 1 or 2, body weight between 50-70 kg and height 150-180 cm, undergoing elective lower limb orthopedic surgery under spinal anesthesia were included. Patients with uncontrolled diabetes mellitus, uncontrolled hypertension, recent myocardial infarction or contraindications to spinal anesthesia were excluded from the study.

All patients were examined a day before surgery and were kept fasting overnight. They received tablet diazepam 5 mg night before surgery and on the morning of surgery with a sip of water as premedication. Patients were randomly allocated to one of the three groups using sealed envelope technique. Group C received 10 mg of 0.5% hyperbaric bupivacaine with 0.2 ml normal saline, Group C_{15} received 10 mg of 0.5% hyperbaric bupivacaine with 15 µg clonidine and 0.1ml normal saline and Group C_{30} received 10 mg of 0.5% hyperbaric bupivacaine with 30 µg clonidine intrathecally. In all the cases, total volume administered intrathecally was 2.2 ml. An Anesthesiologist not involved in the study prepared the test drug solution and observations were made by another Anesthesiologist blinded to the constituents of the test drug.

After shifting patient to the operating table, monitoring in the form of non-invasive blood pressure, which included systolic blood pressure, diastolic blood pressure and mean arterial pressure, continuous electrocardiography and pulse oximetry was instituted and baseline readings were recorded using a multiparameter monitor. Intravenous access was established and patients were coloaded with 10 ml/kg of Ringer lactate solution at the time of performing the block.

L_{3-4} interspace was utilized for performing the subarachnoid block. Quincke spinal needle of 25G (BD Spinal needle, Spain) was used for administration of the test drug solutions for spinal anesthesia. The drugs were injected into the subarachnoid space at the rate of 0.2 ml/s and the needle was removed. The time of completion of spinal injection was designated as time 0 and other time points were measured from this time. Oxygen was administered via facemask to all patients as a routine.

Sensory level of the block was assessed using absolute loss of sensation to pinprick and the highest last level with no sensation to pinprick was recorded as sensory level. Surgeons were asked to proceed once the block level was T_{10}. Motor block in the lower limbs was graded as per modified Bromage grade.

Various parameters were recorded at following points of time like sensory and motor block every 5 min for first 30 min from completion of spinal injection and then every 15 min, highest level of sensory block, time to achieve T_{10} and highest sensory blockade, systolic, mean, diastolic blood pressure and heart rate every 5 min for first 30 min, time to two segment regression of sensory block and regression to T_{12}, time to achieve maximum motor block and time to motor block regression to Bromage grade 3 and complete recovery of motor block.

For sedation, midazolam was administered in doses of 1 mg intravenously as and when required. Epidural supplementation by local anesthetics was done when the patients complained of pain.

Any episode of hypotension during first 30 min after intrathecal drug deposition was recorded. Hypotension was defined as a fall in systolic blood pressure to more than 25% from pre-operative baseline systolic blood pressure and was treated using 3 mg boluses of mephentermine intravenously. Clinically, relevant bradycardia was defined as heart rate <50 beats/min and was treated with atropine 0.6 mg intravenously. Any other intraoperative complication was recorded and managed appropriately.

STATISTICALANALYSIS-

Numbers of participants in this study were calculated considering a minimum augmentation of sensory block by two segments. Minimum of 18 patients were required in each group to produce a significant difference assuming a type-1 error of 0.05 and power of 0.8. Repeated measures analysis of variance was employed to obtain the within and between group comparisons. Annova test was used for multiple comparisons of different groups and different time points with each other and $P < 0.05$ was considered to be significant. Results were expressed in the mean for the level of sensory block and if the central values of mean were different, the mean value was obtained by averaging the two values or higher value of the two was considered as mean. Mean test was applied for their comparison in three groups. In this case, $P < 0.017$ was considered to be significant as per Bonferroni test to obtain the multiple comparisons.

RESULTS-

The mean age, weight and height of patients in each group are shown in Table 1. No significant difference was found between the three groups in relation to these parameters ($P > 0.05$). Durations of surgery were also not found to be statistically significant when compared between Groups C, C_{15} and C_{30} ($P = 0.221$).

Table-1 Patient and operative characteristic in different groups

	Group C (n-20) Mean ± SD	Group C_{15} (n-20) Mean ± SD	Group C_{30} (n-20) Mean ± SD	P value
Age (Years)	66.8 ± 7.4	65.9 ± 7.2	66.2 ± 6.8	0.921
Weight (Kg)	56.3 ± 5.3	55.5 ± 4.9	54.7 ± 5.7	0.637
Height (cm)	171.5 ± 9.1	169.7 ± 8.2	168.9 ± 8.9	0.631
Duration of surgery (min)	84.9 ± 7.1	81.8 ± 8.9	86.1 ± 7.8	0.221

In the present study, considering the type of surgical procedure and the highest dermatomal level for the block, sensory block level of T_{10} was considered as adequate for starting the surgery. Comparison of the mean sensory block levels at different time points showed no significant difference between the three groups until 10 min after spinal injection. Highest sensory level was earlier in Group c 15 and Group C_{30} than Group C as showen in table 2.

Table-2 highest sensory level

	Group C (n=20)	Group C_{15}(2=20)	Group C_{30}(n=20)
	No.	No.	No.
T5	0	0	2
T6	0	2	6
T7	3	10	9
T8	3	4	2
T9	5	3	1
T10	9	1	0

Sensory block characteristics are shown in Table 3. Highest median sensory block level attained in Group C was T_7, T_6 in Group C_{15} and T_5 in Group C_{30}.

Mean times to attain a T_{10} sensory segment block and for sensory block level to regress by two segments was not significantly different between the three groups. There was a significant difference between Groups C_{30} and C and between Groups C_{30} and C_{15} in the mean time to attain highest sensory block level, but no significant difference was observed between Groups C_{15} and C.

The mean time for sensory block to regress to T_{12} sensory level between the three groups showed a significant difference between Groups C_{15} and C and between Groups C_{30} and C. There was no significant difference between Groups C_{15} and C_{30}.

Table-3 Sensory block characteristics in different groups

	Group C (n-20) Mean ± SD	Group C_{15} (n-20) Mean ± SD	Group C_{30} (n-20) Mean ± SD	P value
Time to T10 block (min)	14.8 ± 4.5	11.6 ± 3.1	10.1 ± 2.9	0.001
Highest sensory level (min)	T7	T6	T5	
Time to highest sensory level (min)	15.9 ± 1.8	17.4 ± 4.1	21.4 ± 5.9	o.oo1
Time two segment regression (min)	110.1 ± 18.3	121.0 ± 21.2	141.1 ± 25.5	0.001
Time to regression to T12 level (min)	133.1 ± 27.1	161.3 ± 29.9	196.4± 36.5	0.001

Comparison of motor blockade characteristics in the three groups is shown in Table 4.

Bromage grade 1 was achieved in all the patients in the three groups. No significant difference between the groups was observed. Times taken for motor block to regress to Bromage grade 3 and for complete recovery of motor block (regression to Bromage grade 6) were significantly difference between Groups C_{15} and C and between Groups C_{30} and C, however no significant difference was observed between Groups C_{15} and C_{30}.

Table-4- Comparison of motor blockade characteristics

	Group C (n-20) Mean ± SD	Group C15 (n-20) Mean ± SD	Group C30 (n-20) Mean ± SD	P value
Time to attain max motor block (min)	11.1± 4.2	11.7 ± 3.1	12.9 ± 3.2	0.269
Time to motor regression to Grade 3 (min)	111.8 ± 24.9	136 .6± 31.2	151.3± 41.2	0.002
Time to complete motor block regression (min)	135.2 ± 32.4	159.1 ± 28.3	178.0 ± 35.3	0.001

Comparison of systolic blood pressure at varying time intervals in the three groups was comparable. In all groups, there was a significant fall in mean systolic blood pressure at all time points as compared with the baseline value. On inter-group comparison of systolic blood pressure values, there was no significant difference among them. No significant difference in the trends of diastolic and mean blood pressure on intergroup comparison was observed.

Injection mephentermine was used to treat hypotension in these patients. There was no significant difference in the mean values of heart rate at different time intervals between the three groups.

Although clinically significant bradycardia, which was defined as heart rate less than 50 beats/min, did not occur in any of the cases. Heart rate less than 60 beats/min was noticed in four patients (20%) in Group C_{15} and six patients (30%) in Group C_{30}. The blood pressure was maintained within the normal range at that point of time so no treatment i.e., injection Atropine was required. No patient in any of the groups suffered nausea or vomiting throughout the study period.

DISCUSSION-

In the present study, clonidine in both 15 and 30 µg doses potentiated sensory block levels produced by 10 mg hyperbaric bupivacaine in elderly patients. Clonidine also increased the duration of surgical anesthesia, motor blockade and the duration of analgesia without increasing the incidence of hypotension and other complications.

Clonidine is commonly used because of its safety and various advantages over other adjuvants. The mechanism by which clonidine prolongs motor and sensory block is not well-known. It produces analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.[9] Binding of clonidine to motor neurons in the dorsal horn may prolong motor block.[10]

Its effect in terms of potentiation of sensory and motor block of intrathecal bupivacaine has been studied with doses of 1-2 μg/kg.[11,12] Doses much less than 1 μg/kg have shown contradicting results in terms of augmenting the effects of local anesthetics, but with minimal side-effects in adult patients.[7,8,13] However, the effects and doses of clonidine as adjuvant to intrathecal bupivacaine have not been investigated at length in elderly patients.

van Tuijl *et al*. used 15 and 30 μg of clonidine supplemented to 5 mg hyperbaric bupivacaine for unilateral spinal anesthesia and found no significant difference in the peak sensory block levels, the mean age of their study population was 35-38 years.[8] In another study, similar doses of clonidine were studied with 6 mg bupivacaine for unilateral spinal anesthesia in patients of mean age 56-62 years, the cephalad spread of sensory block was significantly higher by two to four dermatomes.[7] However, no difference in median peak sensory levels was observed when 30 μg clonidine with 12 mg hyperbaric bupivacaine was used in patients with a mean age of 70 ± 6 years.[14] Larger doses of local anesthetics were reported to mask the effect of clonidine on the sensory level.[13]

In the present study, clonidine did not affect the onset of surgical anesthesia, similar results on the onset have been shown by other workers even with slightly higher doses of clonidine.[12] Clonidine in both doses increased the median highest sensory block level, but the time to achieve this level was longer with 30 μg of clonidine. With 15 μg clonidine five patients (26%) had the highest sensory block level of T_5 while with 30 μg nine patients (45%) had the highest spread of sensory block up to T_5 and two patients (10%) had a spread to T_3 level suggesting that clonidine in a dose of 30 μg facilitated the ascent of sensory level block to higher dermatomes for a longer time. Other workers have not reported any effect of adding clonidine to local anesthetics on time to achieve maximum sensory block.[14]

Erturk *et al*. used a low dose hyperbaric bupivacaine of 8 mg with 20 μg fentanyl for hip arthroplasties in geriatric patients and found that dose was adequate for surgical procedures in all patients.[15] In the present study, the dose of hyperbaric bupivacaine used, i.e., 10 mg was chosen 2 mg higher than the above quoted study as the control group would only receive intrathecal bupivacaine without any adjuvant.

Clonidine affects blood pressure in a complex fashion after neuraxial or systemic administration. It produces hypotension by activation of postsynaptic alpha 2 adrenoceptors in the brain stem and by directly inhibiting sympathetic presynaptic alpha 2 adrenoceptors neurons in the spinal cord.[16] In a systemic review, the authors reported a 20% incidence of hypotension in controls and 31.3% incidence (relative risk, 1.81; 95% confidence intervals: 1.44-2.28) in patients receiving clonidine 15-150 μg without evidence of dose responsiveness.[17] Some authors have argued that when large dose of local anesthetic is used it masks the hypotensive effect of clonidine[18] and when comparative large doses of clonidine is used with small doses of local anesthetic the hypotensive effect is revealed.[19] In one study, authors observed that hemodynamic stability is well-maintained in elderly when clonidine 30 μg is used as adjuvant to bupivacaine during the transurethral resection of prostate or bladder tumor.[14] In our study, incidence of hypotension was not increased with use of 15 and 30 μg clonidine probably because of smaller doses of clonidine.

In elderly patients, spinal hypotension is caused predominantly by decrease in the systemic vascular resistance than a decrease in cardiac output,[20] in younger patients systemic vascular resistance decreases to lesser extent for the same level of spinal block.[21] This causes more elderly patients requiring treatment than young.[22] It has also been observed that crystalloid preloading alone may not be sufficient in elderly to compensate for the decrease in systemic vascular resistance.[23] Fluids infusion during first few minutes of block[24] and vasopressors have been suggested to be useful.[25] In the current study, patients were coloaded and vasopressor was used at the first instance when hypotension occurred.

Our study has some limitations. Old patients of ASA status 1-2 were studied, results may not be applicable to patients with significant morbidities. We studied only one dose of bupivacaine with clonidine, same doses of clonidine should be investigated with smaller doses of bupivacaine.

CONCLUSION-

In elderly patients, clonidine when used intrathecally in doses of 15 μg or 30 μg with hyperbaric bupivacaine significantly potentiated the sensory blocks levels and duration of analgesia without affecting the trend of systolic blood pressure. Clonidine in doses of 30 μg however facilitated the ascent of sensory level block to unexpectedly higher dermatomes for a longer time.

REFERENCES

1. 113th ed. Washington D.C: Department of Commerce; 1993. US Bureau of Census. Statistical Abstracts of the United States.
2. Current Population Reports. Washington D.C: Government Printing Office; 1993. Bureau of Census. Sixty-five plus in America.
3. Ferrer-Brechner T. Spinal and epidural anesthesia in the elderly. Semin Anesth. 1986;5:54–61.
4. Racle JP, Benkhadra A, Poy JY, Gleizal B. Spinal analgesia with hyperbaric bupivacaine: Influence of age. Br J Anaesth. 1988;60:508–14.
5. Veering BT, Burm AG, Spierdijk J. Spinal anesthesia with hyperbaric bupivacaine. Effects of age on neural blockade and pharmacokinetics. Br J Anaesth. 1988;60:187–94.
6. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992;76:906–16.
7. Dobrydnjov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: A randomized double-blinded study. Anesth Analg. 2003;96:1496–503.
8. van Tuijl I, Giezeman MJ, Braithwaite SA, Hennis PJ, Kalkman CJ, van Klei WA. Intrathecal low-dose hyperbaric bupivacaine-clonidine combination in outpatient knee arthroscopy: A randomized controlled trial. Acta Anaesthesiol Scand. 2008;52:343–349.
9. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995) Anesthesiology. 1996; 85: 655–74.
10. Smith C, Birnbaum G, Carter JL, Greenstein J, Lublin FD. Tizanidine treatment of spasticity caused by multiple sclerosis: Results of a double-blind, placebo-controlled trial. US tizanidine study group. Neurology. 1994;44:S34–42.
11. Baker A, Klimscha W, Eisenach JC, Li XH, Wildling E, Menth-Chiari WA, et al. Intrathecal clonidine for postoperative analgesia in elderly patients: The influence of baricity on hemodynamic and analgesic effects. Anesth Analg. 2004;99:128–34.
12. Grandhe RP, Wig J, Yaddanapudi LN. Evaluation of bupivacaine-clonidine combination for unilateral anesthesia in lower limb orthipaedic surgery. J Anaesthesiol Clin Pharmacol. 2008;24:155–8.
13. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmström B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: A double-blind, randomized and placebo-controlled study. Acta Anaesthesiol Scand. 2005;49:538–45.
14. 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.
15. Erturk E, Tutuncu C, Eroglu A, Gokben M. Clinical comparison of 12 mg ropivacaine and 8 mg bupivacaine, both with 20 microg fentanyl, in spinal anesthesia for major orthopaedic surgery in geriatric patients. Med Princ Pract. 2010;19:142–7.
16. Hamilton CA. The role of imidazoline receptors in blood pressure regulation. Pharmacol Ther. 1992;54:231–48.
17. 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;33:159–67.
18. Klimscha W, Chiari A, Krafft P, Plattner O, Taslimi R, Mayer N, et al. Hemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. Anesth Analg. 1995;80:322–7.
19. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anaesthesiol Scand. 1994;38:724–8.
20. Nakasuji M, Suh SH, Nomura M, Nakamura M, Imanaka N, Tanaka M, et al. Hypotension from spinal anesthesia in patients aged greater than 80 years is due to a decrease in systemic vascular resistance. J Clin Anesth. 2012;24:201–6.
21. Mark JB, Steele SM. Cardiovascular effects of spinal anesthesia. Int Anesthesiol Clin. 1989;27:31–9.
22. Critchley LA, Stuart JC, Short TG, Gin T. Haemodynamic effects of subarachnoid block in elderly patients. Br J Anaesth. 1994;73:464–70.
23. Riesmeier A, Schellhaass A, Boldt J, Suttner S. Crystalloid/colloid versus crystalloid intravascular volume administration before spinal anesthesia in elderly patients: The influence on cardiac output and stroke volume. Anesth Analg. 2009;108:650–4.
24. Critchley LA, Short TG, Gin T. Hypotension during subarachnoid anesthesia: Haemodynamic analysis of three treatments. Br J Anaesth. 1994;72:151–5.
25. Sharrock NE, Bading B, Mineo R, Blumenfeld JD. Deliberate hypotensive epidural anesthesia for patients with normal and low cardiac output. Anesth Analg. 1994;79:899–904.