ORIGINAL ARTICLE

Response to low-dose intrathecal clonidine in septuagenarians undergoing sub-umbilical surgeries: A study

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ABSTRACT

Clonidine, an alpha-2-adrenergic agonist, may have a clinically relevant analgesic action but also a hypotensive action, when administered spinally. **Aim:** To evaluate the analgesic and circulatory effects of low-dose intrathecal clonidine co-administered with hyperbaric bupivacaine in septuagenarian patients undergoing sub-umbilical surgeries. **Materials and Methods:** A total of 20 patients within the age group of 70-80 years of either sex, enrolled in this study, were randomly divided into groups of 10 each. Group I received clonidine 7.5 μg as an adjuvant to 15 mg of hyperbaric bupivacaine and Group II (control group) received 15 mg of bupivacaine with saline to make volume in the two solutions equal. **Result:** The level of subarachnoid block was comparable in the two groups. Duration of motor blockade was longer in the clonidine group (221.4 ± 35.92 min) compared with the control group (112.3 ± 12.45 min). Request for 1st dose of analgesic was earlier in the control group (135.5 ± 28.52 min) than the clonidine group (295 ± 18.85 min). Mean arterial pressure (clonidine 77.67 ± 6.47 vs. control 93.87 ± 3.03, $P = 0.0002$) and heart rate (clonidine 65.2 ± 5.20 vs. control 77.4 ± 6.06, $P = 0.003$) were significantly lower ($P < 0.05$) in the clonidine group compared with the control group from 20 mins after the block to the end of 3 h. In the clonidine group, 3 patients had postoperative headache, 4 had intra-operative shivering. 2 patients in the clonidine group also developed hypotension and 1 bradycardia and 1 of them developed bradyapnea along with acute hypotension 5 min after shifting to the postoperative ward and later recovered on resuscitation. In the control group 2 patients had bradycardia, 6 had intra-operative shivering and 3 had postoperative headache. **Conclusion:** We conclude that addition of clonidine in the dose of 7.5 μg to bupivacaine significantly increases the duration of spinal analgesia with clinically insignificant influence on hemodynamic parameters.

Key words: *Intrathecal, low-dose clonidine, septuagenarians*

INTRODUCTION

A number of procedures such as combined spinal-epidural technique and/or addition of different adjuvants have been tried intrathecally to prolong and to improve the efficacy of neuraxial/regional analgesia. The agents introduced as adjuvants are adrenergic agonists (clonidine, adrenaline), N-methyl-D-aspartate antagonists (ketamine, magnesium), gamma-aminobutyric acid agonists (midazolam), cyclooxygenase-inhibitors (ketorolac), Ach-esterase inhibitor (neostigmine), Opioids etc.[1] Clonidine, an alpha-2-adrenergic agonist, an effective analgesic, is being extensively evaluated as an alternative to neuraxial opioids used intrathecally for control of pain and has proven to be a potent analgesic, free of at least some of the opioid related side effects.[2]

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Aim

This study was undertaken in the patients who are more vulnerable to the trauma of anesthesia, the septuagenarians, undergoing sub-umbilical surgeries. The aim of this study is to evaluate the effect of addition of a small dose (7.5 μg) clonidine to hyperbaric bupivacaine for spinal anesthesia in the spread and duration of sensory block, duration of motor block,

time to first analgesic request, the degree of analgesia and circulatory effects.

MATERIALS AND METHODS

This prospective study was conducted in a teaching hospital during the period of April 2010 to January 2011. After informing the Ethical Committee and written informed consent was obtained from all the participants, 20 patients of either sex, aged between 70 and 80 years of American Society of Anesthesiologists Grade I and II, undergoing herniorrhaphy, dynamic hip screw fixation for inter-trochanteric fracture femur, open reduction internal fixation for distal femoral fracture, interlocking nailing for fracture tibia and hip replacement were included. The patients having metabolic disorder, psychiatric illness, neurologic disease, on cardiovascular medications, those with history of hypersensitivity to clonidine or local anesthetics, alcoholics, also patients with a body weight of >120 kg, a height of <150 cm, and those with conditions that preclude spinal anesthesia were excluded from the study. Preanesthetic check-up of the patients under the study, were done a day before surgery and were counseled regarding adequate starvation, sedation, local anesthesia, the operative procedures and also were educated about the visual analog scale (VAS)[3] regarding the rate of experience with the analgesia. VAS (0-10 cm).

0	2	4	6	8	10
No pain					Worst pain

Patients were randomly divided equally in two groups of 10 each. Investigations were done according to the institution's protocol. Patients were not premeditated. On arrival in the operation theater, multipara monitor was connected (Philips-Intellivue MP20) for recording the patient's oxygen saturation (SpO_2), heart rate (HR), electrocardiography, noninvasive arterial blood pressure, and respiratory rate. Intravenous (IV) line was established with an 18-G bore cannula and IV preloading was done with 15 ml/kg of Ringer's solution about 15 min before the intended time of intrathecal drug administration. Under all aseptic and antiseptic precautions, spinal anesthesia was administered in sitting position at the L3-L4 interspace using midline approach with a 25 gauge Quincke spinal needle. After ensuring a free flow of cerebro spinal fluid, the Clonidine group (group I) received a single dose of 15 mg of 0.5% bupivacaine (heavy) plus 7.5 μg of preservative free clonidine. The patients in the Control group (group II) were given 15 mg of 0.5% bupivacaine (heavy) mixed with an identical volume of saline. Patient was then made to lie down immediately and the level of sensory block was assessed by pin-prick method using a 25-G short beveled needle and reassessed every 3 min for 15 min to record the highest level of block and the time taken to achieve the highest level. Degree of motor block, at the same intervals as sensory block, was assessed as per modified Bromage scale:[4]

1. Free movement of legs and feet
2. Just able to flex knees with free movement of feet
3. Unable to flex knees, but with free movement of feet
4. Unable to move legs or feet after intrathecal drug injection, data recording was performed during the first half an hour at 5 min interval, then at the 60th min, followed by every hour up to 5th h.

Both the groups were similar in respect of age, body mass index, and duration of surgeries [Table 1]. The baseline values of HR, mean blood pressure (MAP) and blood SpO_2 are presented in Table 2. Table 3 presented a comparison of type of surgery, number and gender in both the groups. The data included the hemodynamic parameters, SpO_2 [Table 2] duration and onset of analgesia which were calculated and compared with baseline values. Time taken to achieve maximum degree of block as per Bromage scale was noted [Table 4]. Intramuscular diclofenac sodium 75 mg was administered as rescue analgesia whenever VAS was >4.[5] The time to first analgesic request (rescue analgesia) was noted. Patients who demanded rescue analgesia intra-operatively were excluded from the study [Table 4].

Descriptive statistics for all continuous variables are denoted as mean (M) and ± standard deviation (SD). The comparisons for testing significant differences between the two groups I and II (for continuous variables) were performed using the Student's *t*-test. While, Chi-square test was used for categorical variables. Statistical significance was set at $P < 0.05$.

Table 1: Patient characteristics data and duration of surgery (mean ± SD and *P* value)

Study material (*n* = 20)	Group I (*n* = 10)	Group II (*n* = 10)	*P*
Age	74.6±3.71	74.8±3.73	0.90
BMI	20.7±2.09	20.3±1.29	0.614
Duration of surgery (min)	83±17.66	79.5±23.14	0.70

Group I: Bupivacaine plus clonidine; Group II: Bupivacaine. BMI: Body mass index; SD: Standard deviation

Table 2: Comparison of baseline vital signs in both groups (mean ± SD and *P* value)

Variables	Group I	Group II	*P*
HR (bpm)	76±4.29	75.2±4.75	0.69
MAP (mmHg)	96.21±3.76	94.60±6.87	0.52
SpO_2 (%)	98.04±2.13	98.52±1.12	0.162

SD: Standard deviation; HR: Heart rate; MAP: Mean arterial pressure; SpO_2: Oxygen saturation

Table 3: Comparison of type of surgery, number and gender in both groups

Type of surgery	Group I			Group II		
	n (%)	Male (%)	Female (%)	*n* (%)	Male (%)	Female (%)
Herniorrhaphy	2 (20)	2 (20)	0	3 (30)	3 (30)	0
Dynamic hip screw	3 (30)	2 (20)	1 (10)	2 (20)	1 (10)	1 (10)
ORIF	2 (20)	1 (10)	1 (10)	1 (10)	0	1 (10)
Interlocking nail	2 (20)	0	2 (20)	3 (30)	1 (10)	2 (20)
Hip replacement	1 (10)	0	1 (10)	1 (10)	0	1 (10)

Response to low-dose intrathecal clonidine in septuagenarians, ORIF: Open reduction internal fixation

Table 4: Time taken for different blocks

Highest level of sensory block	Group I	Group II	*P*
Highest level of sensory block	T6 (T6–T8)	T8 (T7–T10)	
Time (min) taken to achieve highest level	8.4±1.26	12.5±2.54	5.63
Time (min) to achieve maximum Bromage scale	8.7±1.41	13.7±2.66	0.0002
Duration of motor block (min)	221.4±35.92	112.3±12.45	3.90
Time for 1st dose of analgesic	295±18.85	135.5±28.52	1.70

Adverse events like bradycardia (HR <45 bpm), hypotension (drop in systolic blood pressure >20% of baseline or mean arterial pressure (MAP) <60 mmHg sustained for >10 min), nausea, vomiting shivering, pain and also blood loss, urine output, IV fluid input during the procedure were noted. Bradycardia was treated with IV atropine sulfate 0.01 mg/kg, hypotension with trendelenberg position, fluid replacement in the form of Ringer's lactate in calculated doses as per the weight of the patient and further adjusted according to the blood loss during surgery. If there was no response to fluid administration, IV mephentermine sulfate 3 mg aliquots of injection in incremental doses was administered. All patients were observed in the post anesthesia recovery room for 5 h and then in the ward. Severity of pain was measured using a 10 cm VAS at hourly interval for next 24 h by the nursing staff that was unaware of the group the patient belonged to. The first request for pain killer drug was recorded.

RESULT

A total of 20 patients were studied. The variations in the mean HR and arterial pressure have been shown graphically in Figures 1 and 2, respectively. The decrease in mean HR from 20 min until the end of 3 h was greater in clonidine group (65.2 ± 5.20) than in the control group (77.4 ± 6.06) ($P = 0.003$), which is statistically significant ($P < 0.05$). In addition, the decrease from baseline value within the clonidine group was also statistically significant at 5 min to end of 3 h. The MAP also showed a similar trend and there was a significant low MAP in the clonidine group (77.67 ± 6.47), compared with the control group (93.87 ± 3.03) ($P = 0.0002$) from 20 min

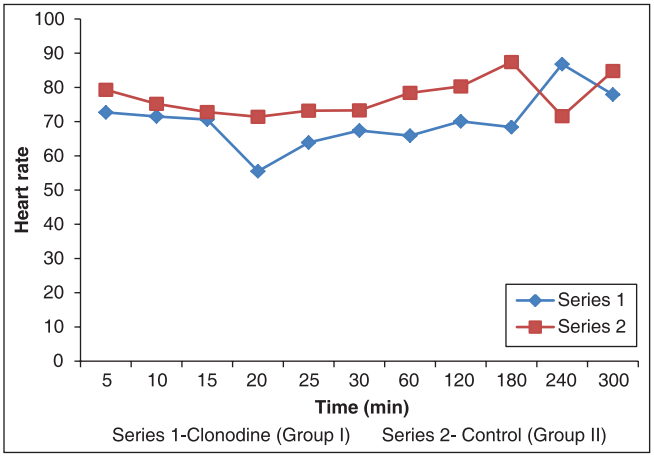

Figure 1: Comparison of heart rate between clonidine group and control group

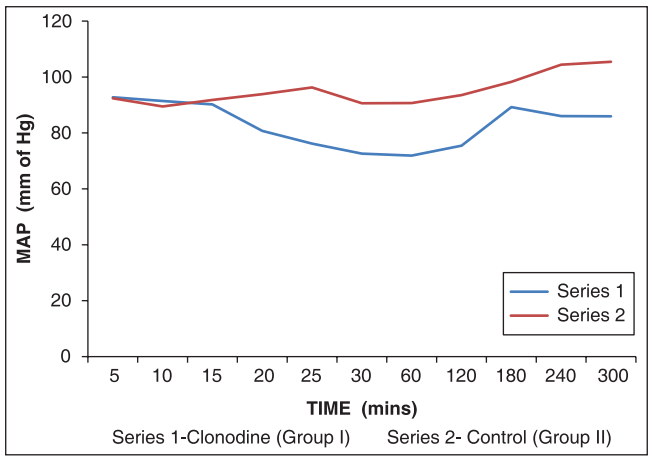

Figure 2: Comparison of mean arterial pressure between clonidine group and control group

after the test drug administration until the end of 3 h ($P < 0.05$).

There was no significant change in respiratory rate and SpO_2 from the baseline in both the groups.

Supplemental oxygen through nasal prongs, at the rate of 2 L/min was administered to all the septuagenarian patients as long as the surgery continued. The parameters regarding onset and regression of sensory block, onset and

regression of motor block were observed and compared (mean ± SD) [Table 4].

A sensory block of T7-T10 and a complete motor blockade of the lower extremities (Bromage 3) were observed in all patients. The mean time to achieve sensory block of T10 was significantly shorter in the clonidine group (8.4 ± 1.26 min) than the control group (12.5 ± 2.54 min). The time of achievement of complete motor block between groups (clonidine group 8.7 ± 1.41 min, control group 13.7 ± 2.66 min), was less in clonidine group and was highly significant ($P = 0.0002$). We also observed that the duration of motor blockade in group I and II was 221.4 ± 35.92 min versus 112.3 ± 12.45 min, which again goes in favor of clonidine.

The first request for supplemental analgesia (VAS scores at >2-3) on regression of sensory block was longer in the clonidine group than in the control group (295 ± 18.85 min vs. 135.5 ± 28.52 min). During the surgical procedures in the control group, incidence of hypotension was nil, 2 had bradycardia, 6 had postoperative shivering and 3 had headache in the postoperative period. In the clonidine group 2 patients had hypotension, 1 had bradycardia, 4 had shivering and 3 had post-operative headache [Figure 3]. 1 patient of hypotension and bradycardia suffered a marked fall in blood pressure and bradyapnea in the postoperative room 5 min after discharge from the operation theater and required emergency resuscitation, later recovered.

DISCUSSION

Clonidine, a centrally acting selective partial agonist for α_2-adrenoreceptor, activates post junctional α_2-adrenoceptors which are located:

a. On primary afferent terminals at peripheral and spinal endings,

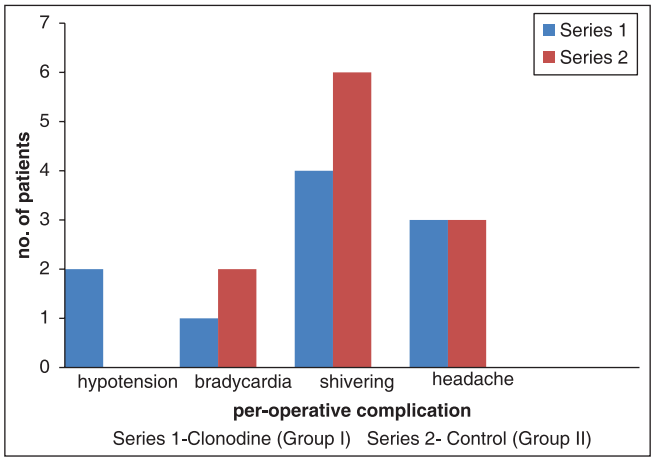

Figure 3: Peroperative complications in the clonidine group and control group

b. On neurons in the superficial laminae of the spinal cord which contain important structures for pain transmission, receiving most of their primary sensory input from Aδ and C fibers and
c. Within several brainstem nuclei implicated in analgesia in the dorsal horn of the spinal cord and thus inhibits nociceptive impulses, the postulated mechanism for which may be that:
    1. Clonidine blocks conduction of Aδ and C fibers and increases potassium conductance in isolated neurons *in vitro*, thus intensifying conduction block.
    2. Clonidine causes local vasoconstriction in the clinical setting, thereby reducing vascular uptake of local anesthetic from around the neural structures.
    3. Clonidine enhances analgesia from intraspinal opioids by interactions within the spinal cord both pre- and postsynaptically.

It was shown that clonidine suppresses the generation of action potentials in tonic-firing spinal dorsal horn neurones, and therefore could contribute to increase both sensory and motor blocks of local anesthetics[6] by 30-50% using doses as high as 1 or 2 μg/kg. This is possibly due to the fact that α_2 adrenoreceptor agonists induce cellular modification in the ventral horn of the spinal cord and facilitate the local anesthetic action. Prolongation in sensory block can be due to vasoconstrictive effect of clonidine.[7] Improved analgesia, at these doses is associated with systemic side effects such as sedation, bradycardia, and hypotension.[8] Following intrathecal administration of clonidine, its analgesic effect is mediated spinally through activation of post synaptic α_2-receptors in substantia gelatinosa of spinal cord.[9,10] Clonidine administered through neuraxial route also has a local effect on sympathetic nerves in the spinal cord.[6] The α_2-adrenergic agonists reduce arterial blood pressure and produce sympathicolysis through effects at specific brainstem nuclei and on sympathetic preganglionic neurons in the spinal cord. These effects are counteracted by direct vasoconstriction resulting from the α_2-adrenergic agonists on the peripheral vasculature. α_2-adrenergic agonists in combination with local anesthetic can potentially increase the degree of sympatholysis resulting hypotension.[11] Clonidine thus affects arterial blood pressure in a complex manner because of opposing actions at multiple sites. Racle *et al.* studied clonidine 150 μg and isobaric bupivacaine with epinephrine in spinal anesthesia for hip surgery, for patients aged 75 years or more and found a decrease in systolic blood pressure of 15% from resting values.[12] Niemi studied clonidine intrathecally in the dose of 3 μg/kg added to 15 mg of 0.5% bupivacaine in patients undergoing knee arthroscopy.[13] Niemi[13] and Acalovschi *et al.*[14] observed significant sedation in their patients because they used higher doses of clonidine.

Filos *et al.* demonstrated that clonidine used intrathecally, as a sole analgesic in doses ≥150 μg maintains relative hemodynamic stability but causes marked sedation.[15] Grace *et al.* and Chiari *et al.* demonstrated that, the optimal dose of intrathecal clonidine in terms of effects versus side effects is controversial in adults.[16,17] Grubb *et al.* found that intrathecal clonidine may provide adjunct analgesia without additional respiratory depression.[18]

De Kock *et al.* recommended a dose of 15-45 μg of clonidine as optimal for supplementing spinal anesthesia.[19]

Dobrydnjov *et al.* added 0, 15, or 30 μg clonidine to 6 mg of intrathecal hyperbaric bupivacaine for inguinal hernia repair and found increase in duration of motor block (146, 155, and 182 min, respectively), but not the duration of analgesia.[7]

Dobrydnjov *et al.*, in another study, performed a double-blinded randomized control trial with low-dose (15 μg) intrathecal clonidine added to local anesthetic in patients during combined spinal-epidural anesthesia for hip arthroplasty and observed a better quality of anesthesia and longer-lasting analgesia.[20] Dobryndjov *et al.* noted postoperative nausea and vomiting in four patients (one each in group B and BC30 and two patients in BC30).[7] Jeon *et al.* found that intrathecal clonidine 150 μg failed to prevent postspinal shivering and confirmed that IV clonidine 1 μg/kg is an effective method to prevent shivering in patients undergoing spinal anesthesia for orthopedic surgery.[21] Dobrydnjov *et al.* recorded 45-120 min after spinal injection, a significant decrease in MAP, but not in HR in groups BC15 and BC30 in comparison to group B.[7] Grandhe *et al.* also observed significant decrease in MAP from 45 min to 8 h after intrathecal injection in groups BC1 and BC2 when compared with group B.[22] Dobryndjov *et al.* and Grandhe *et al.* reported dose dependent sedative effect of clonidine. Wolff *et al.*, had investigated the local anesthetic-like action of clonidine in superficial dorsal horn neurones in his experimental study.[23] Kaabachi *et al.*, used clonidine 1 μg/kg as an adjuvant to plain bupivacaine for spinal anesthesia in adolescents and found the duration of sensory block achieved was prolonged by 30 min and postoperative analgesia by 120 min without severe adverse events.[24] Sethi *et al.* observed that 1 patient in the control group and 3 patients in the clonidine group had nausea, 11 patients complained of dryness of mouth,[8] which was possibly because of a large dose of clonidine (1 mcg/kg) used in their study.

Elia *et al.*, in a systematic review of randomized trials, studied clonidine (15-150 μg) as an adjuvant to intrathecal local anesthetics for surgery and found better intra-operative analgesia, delayed regression of the sensory block as well as the time to first analgesic request and increase in the duration of the motor block. The most prominent adverse effect was intra-operative hypotension.[25]

Van Tuijl *et al.*[26] observed that peak sensory level was comparable among the groups who used higher dose of clonidine but lower dose of bupivacaine. Similar trend of peak sensory level was studied by Grandhe *et al.* despite the use of large dose of clonidine (1 mcg/kg),[22] suggesting that the dose of intrathecal clonidine does not affect the peak sensory level. The data obtained from our study indicates that addition of 7.5 μg of clonidine to 0.5% hyperbaric bupivacaine in a sample size of septuagenarians significantly prolongs the analgesia and motor block and thus reduces the postoperative analgesic requirement. Even though a statistically significant decrease in MAP and HR was noted in the clonidine group compared to the control group, only 1 patient required therapeutic intervention. It is pertinent to mention that the dose of intrathecal clonidine, in our study, is significantly low than the studies conducted by Racle *et al.*,[12] Niemi,[13] Acalovschi *et al.*,[14] Filos *et al.*,[15] De Kock *et al.*,[19] Dobrydnjov *et al.*[7] We observed that peak sensory level was comparable among the groups in our study and the findings were similar to the study conducted by Van Tuijl *et al.*[26] In our study longer duration of analgesia observed was same as with Dobrydnjov *et al.*[20] when their dose of clonidine was 15 μg and motor block was also similar to Dobrydnjov *et al.*[7] when they used even higher doses. Incidence of fall of MAP was there in the studies done by Dobrydnjov *et al.*[7] and Grandhe *et al.*[22] starting from 45 min post spinal, though in our septuagenarians, the fall was from 20 min post spinal but only 1 patient required intervention. No patient in our study complained of dryness of mouth unlike Sethi *et al.*[8] or nausea vomiting unlike Dobrydnjov *et al.*[7] In our study, no septuagenarian was observed having sedation unlike the subjects of Niemi[13] and Acalovschi *et al.*[14] because patients in their studies received clonidine in higher doses. Our study thus implies that it is possible to achieve equally good analgesia without side effects when clonidine is used in dosages as low as 7.5 μg intrathecally.

CONCLUSION

To prolong spinal anesthesia in elderly patients undergoing sub-umbilical surgeries, alternative anesthetic techniques such as epidural or combined spinal-epidural, may be technically difficult and time consuming. In addition, the motor blockade during epidural anesthesia is often not as satisfactory as during spinal anesthesia. So we emphasize on that,

in septuagenarians for sub-umbilical surgeries, the addition of clonidine to bupivacaine in the dose as low as 7.5 μg (approximately 0.15 μg/kg) significantly increases the duration of spinal analgesia with clinically insignificant influence on hemodynamic parameters and level of sedation.

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