

Effect of Clonidine Given by Three Different Routes as Adjuvant to Bupivacaine in Spinal Anaesthesia

Karki Geeta*, Singh Vishwadeep*, Sharma Kailash Chandra**

Abstract

Context: Spinal anaesthesia is the most common method of regional anaesthesia used for lower limb and abdominal surgeries below umbilicus. There is always interest in finding adjuvants that prolong the duration of anaesthesia and analgesia. **Aims:** To evaluate whether clonidine when given by three different routes- oral, intrathecal and intravenous, has any effect on spinal anaesthesia. **Settings and Design:** The study was a prospective, case control study conducted in the department of Anaesthesiology. **Methods and Materials:** All the patients posted for surgery under spinal anaesthesia and who met the selection criteria were randomly then divided into four groups of 30 patients. Group I: Spinal anaesthesia with bupivacaine 3ml. Group II: Spinal anaesthesia with bupivacaine 3 ml + oral clonidine 3µg/kg. Group III: Spinal anaesthesia with bupivacaine 3 ml + intrathecal clonidine 75 µg. Group IV: Spinal anaesthesia with bupivacaine 3 ml + intravenous clonidine 3µg/kg. **Statistical Analysis:** Computer software SPSS version 20 was used for the statistical analysis of the data. For analysis Chi square test and one way ANOVA with bonferroni was used. **Results:** The onset of

sensory and motor block was earlier in oral, intrathecal and intravenous clonidine group as compared to control group. The duration of motor block was longer in oral (154.52±12.18 min), intrathecal (168.80±7.46 min) and intravenous (215.63±26.26 min) clonidine group as compared to control group (149.25±26.42min). Demand for analgesia was delayed in oral (295.81±10.32min), intrathecal (364.80±6.69min) and intravenous group (571.31±8.86min) as compared to the control group (137.50±30.63min). **Conclusion:** Clonidine is a good alternative to opioids as adjuvant to bupivacaine in spinal anaesthesia.

Keywords: Spinal Anaesthesia; Adjuvant. Clonidine; Bupivacaine; Sensory Anaesthesia; Analgesia.

Introduction

Spinal anaesthesia or sub-arachnoid block (SAB), is a form of regional anaesthesia involving injection of local anaesthetic agents into the subarachnoid space through a fine needle. The first spinal analgesia was administered in 1885 by a neurologist named James Leonard Corning when he accidentally pierced the dura

mater while experimenting with cocaine in a dog [1]. The first planned spinal anaesthesia for surgery in man was administered by August Bier in 1898 [2]. Bupivacaine is the local anaesthetic most commonly used for spinal anaesthesia, although lignocaine, tetracaine, ropivacaine, procaine, levobupivacaine and prilocaine can also be used. Local anaesthetics block the generation and the conduction of nerve impulses, by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. The onset of action with bupivacaine is moderate and duration is intermediate. The duration of anaesthesia is longer with bupivacaine than with any other commonly used local anaesthetic. It has also been noticed that after spinal anaesthesia there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

Author's Affiliation:

*Assistant Professor **Professor,
Department of Anaesthesiology, Sri
Ram Murti Institute of Medical
Sciences, Bareilly, India.

Corresponding Author:

Geeta Karki, Flat No. A-1,
Doctor's Residence, SRMS IMS,
Bhojipura, Bareilly, U.P -243202.
E-mail: krkgits@gmail.com

Received on 27.03.2017

Accepted on 07.04.2017

Clonidine, an imidazoline derivative centrally acting α_2 -adrenergic agonist. It crosses the blood brain barrier and acts in the hypothalamus to induce a decrease in blood pressure. Clonidine stimulates all three α_2 receptor subtypes with similar potency. α_2 receptors also mediate essential components of the analgesic effect of nitrous oxide in the spinal cord. Clonidine is also a potent sedative and analgesic. Clonidine functions as a sympatholytic by stimulating presynaptic α_2 -receptors leading to decreased release of norepinephrine at both central and peripheral adrenergic terminals. In addition to its influence on the autonomic nervous system, it is well established that clonidine is an effective analgesic, and this is also attributable to its α_2 -agonist activity. A tremendous amount of modulation of incoming pain signals occurs in the dorsal horn of the spinal cord prior to being sent to higher centers in the CNS. Nociceptive stimuli promote release of excitatory transmitters from primary afferents in the dorsal horn. To compensate, there is simultaneous release of norepinephrine from descending inhibitory neurons, which binds to α_2 -receptors in the dorsal horn to diminish after pain transmission, thereby producing analgesia. Thus, it is obvious that drugs acting on α_2 -receptors should influence the transmission and perception of pain. Therefore, it is the mimicking of the actions of descending inhibitory fibres by which clonidine, and all α_2 -agonists, causes analgesia. As cholinergic activation in the dorsal horn has also been shown to impart analgesia and clonidine increases Ach levels in lumbar CSF. Thus, α_2 -agonists impart analgesia through both cholinergic and noradrenergic transmission.

Clonidine also potentiates sensory and motor blockade of epidural and peripheral nerve block. Three mechanisms for this have been given. First, clonidine has intrinsic ability to block conduction in C and A δ fibres and will intensify conduction block of local anaesthetics. Second, clonidine may cause local vasoconstriction and thus impair vascular removal of epidural local anaesthetics. Third, it has been shown that any analgesic, whether neuraxial or systemic, will augment peripheral or spinal blockade.

Our aim in this study is to evaluate whether clonidine when given by three different routes- oral, intrathecal and intravenous, has any effect on spinal anaesthesia, by comparing the onset and duration of sensory and motor block and duration of post operative analgesia.

Material and Methods

After clearance from the ethical committee of the institute, this prospective, randomised case control study was started in the anaesthesiology department. The patients were selected for the study after fulfilling the following selection criteria.

Inclusion Criteria

1. ASA grade 1 and 2
2. Age between 20 and 60 years.
3. Posted for elective lower abdominal surgery
4. Informed consent given

Exclusion Criteria

1. Patients with hypertension/taking antihypertensive drugs
2. History of hypersensitivity to local anaesthetics or clonidine
3. Body weight greater than 120 kg or less than 40 kg.
4. Height less than 140 cm.
5. Any neurological disorder
6. Any contraindication to spinal anaesthesia.
7. Pregnancy.

Sample Size Estimation

Calculation of the number of patients to be selected for the study was calculated according to the normal distribution theory. A minimum of 25 patients were required with fixation of type 1 error (α) at 0.05 and the power of study ($1-\beta$) at 0.8. Hence, we decided to take 30 patients in each group.

All the patients posted for surgery under spinal anaesthesia and who met the selection criteria were randomly then divided into four groups of 30 patients each.

Group I : Spinal anaesthesia with 0.5% heavy bupivacaine 3ml (15 mg)

Group II : Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg) + oral clonidine 3 μ g/kg

Group III : Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg) + intrathecal clonidine 75 μ g

Group IV : Spinal anaesthesia with 0.5% heavy bupivacaine 3 ml (15 mg) + intravenous clonidine 3 μ g/kg

All the patients went through pre anaesthetic check up a day before surgery which included a detailed history, physical examination and appropriate investigations as per requirement. On the day of surgery, after shifting the patient to the OT, an intravenous access was attained and patient was preloaded with 20 ml/kg of crystalloid solution (Ringer Lactate). Standard anaesthetic monitors like Pulse oximetry, ECG and Non invasive blood pressure were attached. After all aseptic precautions, lumbar puncture was performed in sitting position at L2-3/3-4 intervertebral space with a 25 gauge Quincke's spinal needle. After free flow of CSF, 3 ml of heavy bupivacaine 0.5% was given in all the four groups. Along with it, in Group I 0.5 ml of intrathecal saline was given, in Group II 75 µg clonidine was given, in Group III clonidine 3µg/kg was given orally 60 min before the procedure and in Group IV clonidine 3µg/kg diluted to 5 ml was given intravenously slowly over 8-10 minutes after performing the subarachnoid block. After the block the patient was again made to lie supine and vitals (Heart rate, systolic and diastolic blood pressure and mean arterial pressure) were monitored at regular intervals – every 5 min for the first half an hour and then every 15 min till the end of surgery. Sensory block was assessed by response to pin prick. Onset of sensory anaesthesia was defined as the time from the block given to no pain to pin prick at T 10. Motor block was assessed by the Bromage scale. Motor block onset was defined as the time from the block to score of Bromage 2.

Sedation was assessed by Ramsay sedation scale and analgesia was assessed by VAS. Intraoperative vitals of the patient, any adverse effects and total duration of surgery was noted. In the postoperative period, the time for the demand of first analgesic was noted. Duration of analgesia was defined as the time

from block to the time for first analgesic demand by the patient in the postoperative period. Duration of sensory block was taken as the time for regression of sensory block to L1 level and duration of motor block was taken as the time for regression of motor block to a score of Bromage 0.

Statistical Analysis

Computer software SPSS version 20 was used for the statistical analysis of the data. For analysis of demographic data Chi square test was used and comparison of the groups for block characteristics was done by one way ANOVA with bonferroni . A p value of 0.05 or less was considered as statistically significant.

Observations and Results

The aim of our study was to compare the effect of clonidine given by different routes on the block characteristics of spinal anaesthesia.

Table 1 shows the demographic characteristics of the groups. The mean age of patients in Group I was 39.95 years, in Group II was 40.76 years , in Group III was 38.68 years and in Group IV was 41.88 years. All the groups were comparable with respect to age. Out of 30 patients in Group I , 14 were male and 16 were female, in Group II, 13 were male and 17 were female, in Group III there were 15 male and 15 female patients and in Group IV there were 16 male and 14 female patients. The groups were comparable with respect to age. As shown in Table 1, the mean weight of patients in Group I was 60.50 kg, in Group II was 59.36 kg , in Group III was 61.08 kg and in Group IV was 57.25 kg. There was no statistically significant

Table 1: Demographic profile of study patients.

	Group I (Control)	Group II (Oral)	Group III (Intrathecal)	Group IV (Intravenous)	P value
Age (Years)	39.95± 12.02	40.76 ± 13.427	38.68± 12.13	41.88 ± 13.579	0.73
Sex (M:F)	14:16	13:17	15:15	16:14	0.57
Weight (KG)	60.50 ± 10.314	59.36 ± 11.214	61.08 ± 8.698	57.25 ± 6.933	0.38
Height (CM)	159.70 ± 8.247	158.67 ± 9.257	161.44± 7.53	160.13 ± 7.9	0.74
BMI	23.59 ± 2.57	22.57 ± 1.98	23.36 ± 2.35	22.29 ± 1.80	0.21

Table 2: Baseline parameters of patients

	Group I	Group II	Group III	Group IV	P Value
SPO2	99.65 ± 0.484	99.53 ± 0.469	99.72 ± 0.458	99.47 ± 0.743	0.37
HR	82.95 ± 9.698	86.22 ± 8.469	85.12 ± 9.471	79.31 ± 15.713	0.29
SBP	127.70 ± 12.80	126.78 ± 10.812	126.64 ± 13.784	128.20 ± 15.20	0.93
DBP	74.20 ± 7.592	72.78 ± 7.812	73.68 ± 6.77	75.93 ± 8.51	0.64

Table 3: Block characteristics in the study groups

	Group I	Group II	Group III	Group IV	P Value
Sensory Onset (Min)	5.32 ± 0.67	5.20 ± 0.73	4.32 ± 0.81	3.25 ± 0.72	<0.001
Motor Onset (Min)	10.10 ± 2.99	7.25 ± 0.79	7.12 ± 2.39	6.44 ± 2.16	<0.001
Sensory Duration (Min)	169.75 ± 26.16	182.47 ± 21.13	191.20 ± 19.39	293.75 ± 19.45	<0.001
Motor Duration (Min)	149.25 ± 26.42	154.52 ± 12.18	168.80 ± 7.46	215.63 ± 26.26	<0.001
Demand For Analgesia (Min)	137.50 ± 30.63	295.81 ± 10.32	364.80 ± 6.69	571.31 ± 8.86	<0.001

Table 4: Incidence of side effects

	Group I	Group II	Group III	Group IV
Bradycardia	4	4	5	6
Dry Mouth	0	0	1	2
Hypotension	6	5	12	25
Sedation	0	5	7	23
Shivering	9	0	2	2

difference in weight in the four groups. As is evident from the table, the four groups were comparable with respect to height and BMI also.

Table 2 shows the baseline parameters in the four groups. The baseline SpO₂ in Group I was 99.65%, in Group II was 99.53 %, in Group III was 99.72% and in Group IV was 99.47 %. The mean heart rate in Group I was 82.95 beats per minute , in Group II was 86.22 beats per minute, in Group III was 85.12 beats per minute and Group IV was 79.31 beats per minute. The mean systolic blood pressure in Group I was 127.70 mm of Hg, in Group II was 126.78 mm of Hg , in Group III was 126.64 mm of Hg and in Group IV was 128.20 mm of Hg. The mean diastolic blood pressure in Group I was 74.20 mm of Hg, in Group II was 72.78 mm of Hg, in Group III was 73.68 mm of Hg and in Group IV was 75.93 mm of Hg. All the four groups were comparable with respect to baseline parameters.

Table 3 shows the block characteristics. As shown in table, the mean time of onset of sensory block in Group I was 5.32 minutes, in Group II was 5.20 minutes, in Group III was 4.32 minutes and in Group IV it was 3.25 minutes. The sensory onset is significantly earlier than the control group ($p < 0.001$). The mean time of onset of motor block was 10.10 minutes in Group I, 7.25 minutes in Group II, 7.12 minutes in Group III and 6.44 minutes in Group IV. The motor block onset is significantly faster than the control group ($p < 0.001$). The mean time of duration of sensory block was 169.75 minutes in Group I, 182.47 minutes in Group II, 191.20 minutes in Group III and 293.75 minutes in Group IV ($p < 0.001$). The mean duration of motor block was 149.25 minutes in Group I, 154.52 minutes in Group II, 168.80 minutes in Group III and 215.63 minutes in Group IV ($p < 0.001$). The mean time for demand of analgesia was 137.50 minutes in Group I, 295.81 minutes for Group II, 364.80 minutes in Group III was 364.80 minutes and in Group IV was 571.31 minutes ($p < 0.001$).

Table 4 shows the incidence of side effects in the four groups. In Group I, bradycardia was seen in 4 patients, hypotension in 6 patients and 9 patients had shivering. In Group II, 4 patients had bradycardia, and 5 patients each had hypotension and sedation as side effect. In Group III, 5 patients had bradycardia, 1 patient complained of dry mouth, 12 patients had hypotension, 7 patients had sedation and 2 patients experienced shivering. In Group IV, 6 patients had bradycardia, 25 patients had hypotension, 23 patients had sedation and 2 patients experienced shivering as side effect.

Discussion

Vasoconstrictors have been used since ages as adjuncts to local anaesthetics for prolongation of spinal anaesthesia. In addition to vasoconstrictor, intrathecal opioids, α_2 -agonists like dexmedetomidine and clonidine are also effective in prolonging the local anaesthetic induced sensory and motor blockade.

The present study was designed to study the effect of clonidine on spinal anaesthesia when given as adjuvant by intrathecal, oral and intravenous routes with intrathecal bupivacaine 0.5% with respect to onset and duration of sensory and motor block, duration of analgesia, time for demand of analgesic and side effects.

The present study was carried out on 120 patients of ASA grade 1 and 2 of either sex aged between 18 and 60 years scheduled for elective surgery under spinal anaesthesia.

Effect of Oral Clonidine

In our study it was found that oral clonidine 3 μ g/

kg when given 60 minute before subarachnoid block, resulted in a faster onset of sensory and motor block, longer duration of sensory and motor block and prolonged duration of analgesia in the postoperative period. The results are similar to those observed in previous studies [3-6]. While Ota et al [4] reported that oral clonidine prolong the duration of tetracaine sensory analgesia by 93%, Bonnet et al [5] failed to demonstrate significant prolongation of bupivacaine induced sensory and motor blockade following clonidine 150 µg or 0.3 mg orally. Suganthi K S and Kalyansundaram K [6] studied the effects of oral clonidine on spinal anaesthesia and found that sensory blockade was prolonged by 56% and motor blockade by 39% in the oral clonidine group. In this study it was found that oral clonidine 150 µg decreased the time taken for attainment of highest level of sensory blockade to 9.13 minutes when compared to placebo group in which it was 13 minutes. However, oral clonidine did not affect the onset of complete motor blockade.

Clonidine has been demonstrated to inhibit neurotransmission in both A-delta and C nerve fibre which are theorized to mediate pin prick and surgical pain. It has also been demonstrated to potentiate inhibitory effects of local anaesthetics on C fibre activity. Therefore clonidine may exert its effects within the central nervous system at peripheral nerve roots by potentiation of effects of local anaesthetics.

Effect of Intrathecal Clonidine

In the present study 75µg clonidine when given with 15mg of bupivacaine 0.5% intrathecally, resulted in faster onset of sensory and motor block as compared to the control and oral clonidine group. Intrathecal clonidine group had a significantly longer duration of sensory and motor block than the control and oral group. The patients in intrathecal group had a delayed demand for analgesia in the immediate postoperative period. These findings are in concurrence with the findings in earlier studies [7-13]. Racle et al [7] demonstrated that intrathecal clonidine 150 µg prolonged motor blockade by 38% and sensory blockade by 46% when used as an adunct to spinal anaesthesia with bupivacaine. Victor Whizat-Lugo et al [8] compared dexmedetomidine and clonidine as adjuvant in spinal anaesthesia and observed that both prolong the duration of spinal anaesthesia. The duration of sensory blockade was increased by one hour and motor blockade by 20 minutes in the clonidine group. Study by L. Niemi [9] using 3µg/kg clonidine intrathecal with bupivacaine spinal anaesthesia

showed lower blood pressure and heart rate in the clonidine group than in control group. He found that with intrathecal clonidine the duration of bupivacaine spinal anaesthesia was significantly prolonged.

The mechanism by which intrathecal α_2 -agonists prolong the motor and sensory block is under speculation. It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anaesthetics and intrathecal α_2 -agonists. Local anaesthetics act by blocking sodium channels, α_2 -agonists act by binding to the presynaptic C-fibres and postsynaptic dorsal horn neurons. They produce analgesia by depressing release of C-fibre transmitters and by hyperpolarisation of post synaptic dorsal horn neurons.

Effect of Intravenous Clonidine

In our study the patients receiving intravenous clonidine experienced a faster onset of sensory and motor block, a significantly longer duration of block and delayed requirement for analgesic in the postoperative period. Similar findings have been observed in the studies conducted in past. Study conducted by Prerana N Shah using 3µg/kg intravenous clonidine with bupivacaine spinal anaesthesia showed that the sensory and motor blockade duration was significantly prolonged in the clonidine group as compared to the saline group [14]. Rhee K et al [15] in 2003 studied the effect of intravenous clonidine on duration of spinal anaesthesia. They observed that the duration of sensory and motor block was longer in clonidine group compared with the control group and the incidence of bradycardia and hypotension was not different in the two groups. They concluded that when given within 1 hour of spinal block, intravenous clonidine prolonged bupivacaine spinal anaesthesia. V.S. Reddy et al [16] compared and evaluated the efficacy of intravenous dexmedetomidine with clonidine and placebo on spinal blockade duration, postoperative analgesia and sedation in patients undergoing surgery in bupivacaine spinal block. They concluded that single dose intravenous dexmedetomidine resulted in early onset, rapid establishment of sensory and motor blockade, prolongation of analgesia into the postoperative period and stable cardiovascular parameters.

The analgesia produced by α_2 -agonists like clonidine is due to their action at spinal, supra-spinal, direct analgesic and/or vasoconstricting actions on blood vessels [17]. The locus coeruleus and the dorsal raphe nucleus are the important central neural structures where these drugs act to produce sedation

and analgesia [18]. This supra-spinal action can explain the prolongation of spinal anaesthesia after administration of clonidine intravenously. The mechanism of motor block produced by α_2 agonist is unclear but there is some evidence that clonidine results in direct inhibition of impulse conduction in the large, myelinated A- α fibers.

In our study, two segment regression time of sensory block and time of first request for analgesic in the intravenous clonidine group was prolonged significantly. This can be explained by the affinity of clonidine for α_2 receptors. The mechanism for prolongation of motor block by clonidine is unclear but there is speculation that it may be due to direct inhibition of impulse conduction in the large, myelinated A- α fibers.

Incidence of Side Effects

In our study, hypotension was the most common side effect observed in all the four groups, with highest incidence in the intravenous clonidine group followed by intrathecal clonidine group. Sedation was most common in the intravenous group followed by intrathecal group. Bradycardia was common in all the four groups. Shivering was most common in the control group.

The hemodynamic changes that is hypotension and bradycardia are explained due to decrease in central sympathetic outflow as observed in study conducted by Filos KS et al [19]. Liu et al [3] used oral clonidine with lidocaine spinal anaesthesia and observed that there was no significant decrease in blood pressure in the oral clonidine group.

It is not clear whether the effect of clonidine is mediated locally at the level of the spinal cord or whether the effect is mediated systemically. IV clonidine achieves higher plasma concentrations and more rapidly than oral clonidine and intrathecal injection. The mechanism of prolongation of sensory and motor block by clonidine is not known. It is speculated that the mechanism of analgesia is depression of transmitter release from C-fibres and postsynaptic dorsal horn neuron hyperpolarisation. Motor block prolongation is due to binding of clonidine to motor neurons in the dorsal horn.

Conclusion

We can conclude from this study that clonidine when given by various routes- intrathecal, intravenous and oral, along with spinal anaesthesia

results in early onset, prolonged duration of sensory and motor block and prolonged analgesia in immediate postoperative period with no significant increase in the incidence of side effects. Thus, clonidine is a good alternative choice as adjuvant to spinal anaesthesia in addition to opioids.

References

1. Corning JL. Spinal anaesthesia and local medication of the cord. NY Med J. 1885; 42:483-5.
2. Bier A. Versuche uber Cocainisierung des Ruckenmarkes (Experiments on cocainization of the spinal cord. Dtsche Z Chir. 1899; 51:361-9.
3. Liu, Spencer MD. Oral clonidine prolongs lidocaine spinal anaesthesia in human volunteers. Anesthesiology 1995; 82:1353-59.
4. Ota K, Namiki A, Iwasaki H, Takahashi I. Dosing interval for prolongation of tetracaine spinal anaesthesia by oral clonidine in humans. Anesth Analg. 1994; 79(6):1117-20.
5. Bonnet F, Buisson VB, Francois Y, et al. Effects of oral and subarachnoid clonidine on spinal anaesthesia with bupivacaine. Reg Anesth. 1990; 15:211-4.
6. Suganthi KS and Kalyansundaram K. Effects of oral clonidine premedication on the onset and duration of spinal anesthesia with hyperbaric bupivacaine a prospective, double blind, randomized, controlled study. IOSR Journal of Dental and Medical Sciences. 2016; 4(15):8-14.
7. Racle JP, Benkhadra A, Poy JY, et al. Prolongation of isobaric bupivacaine spinal anaesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg. 1987; 66:442-6.
8. Victor Whizar-Lugo, Irma A, Gomez-Ramirez, Roberto Cisneros-corrall, Nora Martinez-Gallegos. Intravenous dexmedetomidine vs intravenous clonidine to prolong bupivacaine spinal anesthesia. A double blind study. Anestesia en Mexico. 2007; 19:143-46.
9. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anesthesia, hemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anaesthesiol Scand 1994; 38:724-8.
10. Dobrydnjov I, Axelsson K, Thorn SE, Matthiesen P, Klockhoff H, Holmstorm B, et al. Clonidine combined with small dose bupivacaine during spinal anaesthesia for inguinal herniorrhaphy : A randomised double blinded study. Anesth Analg. 2003; 96:1496-503.
11. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as

- adjuvant to bupivacaine. *Indian J Anaesth.* 2007; 51:415.
12. Grace D, Bunting H , Milligan KR, et al. Postoperative analgesia after coadministration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement. *Anesth Analg.*1995; 80:86-91.
 13. Agreta Gecaj-Gashi, Hasime Terziqi, Tune Pervorfi and Arben Kryeziu. Intrathecal clonidine added to small dose bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery. *Can Urol Assoc J.* 2012; 6(1):25-29.
 14. Prerana N. Shah and Devanand Pawar. Use of intravenous clonidine for prolonging spinal anaesthesia. *Global Journal of Medical Research: I surgeries and cardiovascular system.* 2014; 1(14).
 15. Rhee K , Kang K , Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. *Acta Anaesthesiol Scand.* 2003; 47(8):1001-5.
 16. Reddy VS , Shaik NA, Donthu B, Sannala VKR and Venkatsiva Jangam. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: A randomized double blind study. *J Anaesthesiol Clin Pharmacol.* 2013; 29(3):342-7.
 17. Reddy SVR , Yaksh TL . Spinal noradrenergic terminal system mediates antinociception. *Brain Res.*1980; 189:391-401.
 18. Erne-Brand F , Jirounek P, Drewe J , et al. Mechanism of antinociceptive action of clonidine in nonmyelinated nerve fibres. *Eur J Pharmacol.* 1999; 383:1-8.
 19. Filos KS, Goudas LC , Patroni O, et al. Hemodynamic and analgesic profile after intrathecal clonidine in humans: a dose response study. *Anesthesiology.* 1994; 81:591-601.
-