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A Comparative Study between Intrathecal Bupivacaine with Clonidine vs Bupivacaine with Neostigmine for Vaginal Hysterectomies: A Randomized Double Blinded Study

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Abstract

Introduction: Vaginal hysterectomy is the most common surgery done under spinal anaesthesia. The combination of local anaesthetics with adjuvants is getting more popular for better post-operative analgesia. *Aim:* The purpose of our study is to evaluate and compare the addition of clonidine and neostigmine to intrathecal bupivacaine for prolongation of post-operative analgesia. *Materials & Methods:* This was a prospective, randomized, controlled, double blind study carried out in patients undergoing vaginal hysterectomies. 50 patients of ASA grade I & II between 45-60years of age were assigned to 2 groups. Group BC: received 0.5ml of intrathecal clonidine (75µg) along with 2.5ml of 0.5% Bupivacaine Group BN: received 0.5ml of intrathecal neostigmine(50µg) along with 2.5ml of 0.5%bupivacaine. *Results:* Sensory block onset, level of sensory block, duration of analgesia, motor block onset, duration of motor block, degree of motor block and recovery from motor block and incidence of side-effects are evaluated. *Conclusion:* We concludefrom our study that intrathecal neostigmine 50µg added to 12.5 mg hyperbaric bupivacaine significantly hastens the onset of sensory and motor block when compared to 75µg clonidine and duration of analgesia is more prolonged with clonidine than neostigmine.

Keywords: Neostigmine; Clonidine; Post-Operative Analgesia.

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Introduction

Vaginal hysterectomy is the most common surgical procedure done under spinal anaesthesia. Regional anaesthesia in particular spinal anaesthesia was widely used nowadays to perform surgeries of lower abdomen and lower extremities. Several studies proved that regional anaesthesia produces less blood loss and there will be decreased incidence of deep vein thrombosis, allows improved pain relief and devoid of adverse effects of general anaesthesia like nausea, sorethroat and altered mental status and cognisive dysfunction. Regional anaesthesia also leads to good pain relief ranging from few hours to several hours. Goodpain

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relief results in short hospital stay and improved patient ability during postoperative period.

Local anaesthetics are commonly used for regional anaesthesia, but due to their short duration of action may lead to early postoperative analgesic requirement. Several therapeutic regimens i.e local anaesthetics along with adjuvants have been tried for intra and postoperative pain relief and increasing regional anaesthetic period but no drug have been identified without associated side effects [1]. Various drugs that can be added to local anaestheticsinclude opioids and nonopioids drugs.

Clonidine is a selective partial agonist for α_2 adrenergic receptors, the analgesic effect following its intrathecal administration is mediated spinally through the activation of postsynaptic α_2 receptors in substantia gelatinosa of the spinal cord. The intrathecal administration of clonidine prolongs both sensory and motor block and also post operative analgesia [2].

Neostigmine is one of nonopioid, anticholinesterase agent used to produce analgesia by activating descending pain inhibitory pathways [3]. It acts by increasing acetylcholine at synapses. Both clonidine and neostigmine have shown effect withlocal anaesthetics, so we considered these two drugs as adjuvants to local anaesthetics and compared their equivalent doses effects.

The purpose of the study was to asses the anaesthetic effects of both clonidine and neostigmine as adjuvants to local anaesthetic Bupivacaine given intrathecally in patients undergoing vaginal hysterectomies.

Materials & Methods

After ethical committee approval 50 patient of ASA grade I & II, aged between 45 to 60 years were assigned to 2 groups by computer generated randomization table. This was a prospective randomized double blinded study performed in our institute from June 2017 to January 2018. Informed consent was taken.

Exclusion criteria include those contraindicated for regional anaesthesia including local infection, haemorrhagic disorders, drug hypersensitivity, muscular disorders and central and peripheral neuropathies and known allergy to study drugs.The selected patients were divided into two groups.

Group BC-received 0.5ml of intrathecal clonidine 75 μg+2.5ml of 0.5%hyperbaric Bupivacaine.

Group BN-received 0.5ml of intrathecal neostigmine 50μg+2.5ml of 0.5% hyperbaric Bupivacaine.

The volume of the solution given intrathecally is 3ml in both groups. The patient and the monitoring anaesthesiologist were blinded to the study solutions. Intravenous line was secured and all the patients were preloaded with 10ml of ringer lactate. The standard monitoring included ECG, pulseoximetry and NIBP and the base line parameters are recorded prior tospinal blockade. Spinal blockade was done in lateral position, at L_3-L_4 level by midline approach with 25G Quinkie' s needle and the study drug was injected after free flow of CSF. After the intrathecal injection, patient repositioned in supine position. After subarachnoid block the following parameters were noted.

Sensory block onset, level of block, the motor block onset and completion of motor block, and recovery from block, total duration of analgesia i.e. time from onset of analgesia to the point where the patient complains of pain or requiring rescue analgesics or visual analog scale (VAS>4) were noted. Sensory block was assessed byusing pinprick test. Motor block was evaluated by Modified Bromage scale as below:

0- Without motor block.

1- Impossibility of hip flexion

2- Impossibility of knee flexion

3- Impossibility of ankle flexion.

The intraoperative and recovery phase complications like nausea, vomiting,itching, dysnoea, respiratory rate less than 10/mt, hypoxia, bradycardia, and hypotension were recorded.

Statistical Analysis

The data arepresented as mean and standard deviation. All categorial data analysed using Fischer exact test and Chi-Square test as required and continuous variables using Student 't' test. Value of $p<0.05$ was considered significant. Graph pad prism version 7 (California corp.inc) was used for statistical analysis.

Results

The mean age in Group BC was 48±6yrs and in Group BN is 52±8 yrs. The mean weight in Group BC was 50±4kgs and in Group BNwas 52±6 kgs and the mean height in Group BC was 150±5cms and in Group BN was 150±5cms. So the demographics and duration of surgery were comparable between the two groups. (Table 1).

Table 1:

	Group BC	Group BN
Age	48±8	52±8
Weight	50±4	52±6
Height	150±5	150±5

The mean time of onset of sensory blockade was 140±15 secs in Group BC and in Group BN was 85±20 secs with p value of <0.05 which is stastistically significant. The mean time of onset of motor block was 200±20 secs in Group BC and in Group BN was100±15 secswith p value of <0.05 which is stastistically significant. The mean total duration of sensory block was 302±30 mintsin Group BC and in Group BN was 260±20 mts with p value of < 0.05 which is highly significant. The mean total duration of motor block was 200±40 mts in Group BC and in Group BN was 180±30 mts. (Table 2 and 3).

The mean time for rescue analgesic was longer for Group BC when compared with patients in Group BN ($p < 0.05$). Group BN patients has significantly higher overall 24hrs VAS scores when compared to patients in Group BC ($p< 0.05$). (Graph 1).

Bradycardia is seen in both groups with no significant difference. 5 pts in clonidine & 6 pts in neostigmine required atropine. Hypotension is significantly higher in BC group (15 compared to 5) than BN group and required intervention with mephentermine 6mg. (Graph 2).

Sedation scores are significantly higher in BC (RSS 4) than BN (2) group. Respiratory depression was not noted in both the groups.

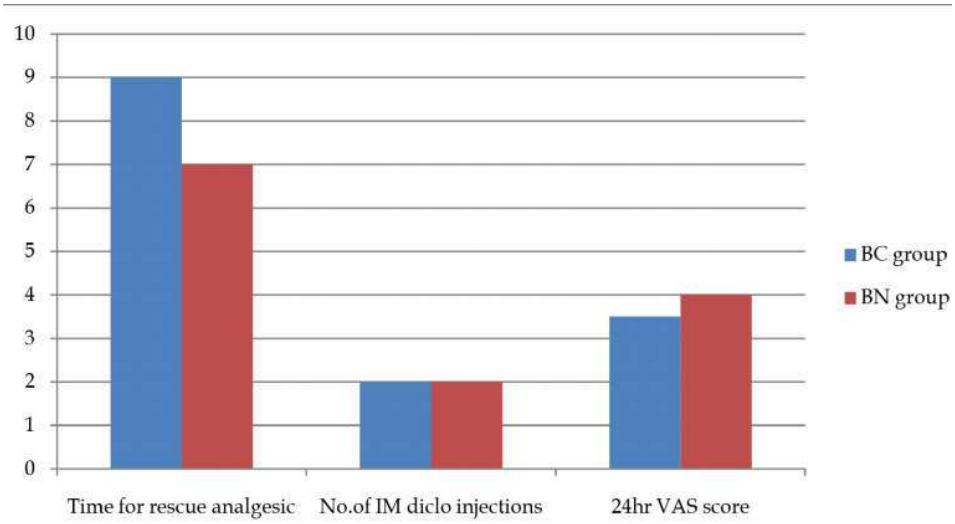
PONV is significantly higher in BN (4) than BC (2) group.

Table 2: Sensory characteristics

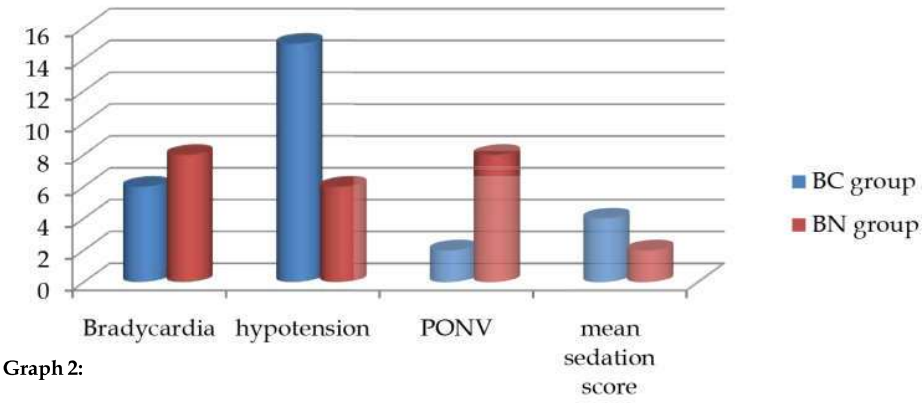
Variable	Group BC	Group BN	P value
Mean onset time	140±15 secs,	85±20 secs,	0.0001
Mean cephalad spread	T6	T6	
Mean total duration of absolute analegesia	302±30 mins	260±20 mins	0.0002

Table 3: Motor Characteristics

Variable	Group BC	Group BN	P value
Mean time to attain max motor block	200±20 secs,	100±15 secs,	0.0001
Quality of block	Bormage grade III→100%	Bormage grade III→100%	
Duration of block	200±40 mins	180±30 mins	0.0001



Graph 1:



Graph 2:

Discussion

Our study results shows that low dose of intrathecal Neostigmine added to intrathecal Bupivacaine increased the mean time of onset of sensory and motor blockade when compared to low dose of Clonidine added to intrathecal bupivacaine and also there is prolongation of duration of analgesia with low dose clonidine when compared to intrathecal Neostigmine combined with bupivacaine.

Clonidine is a selective partial agonist for $\alpha_2$adrenergic receptors. Intrathecal clonidine produced analgesia is mediated through activation of postsynaptic α_2 receptors in subtantiagelatinosa of spinal cord [4].

Several previous studies proved that intrathecal clonidine combined with local anaesthetics and opioids can be used for labour analgesia and orthopaedic surgeries [5-7]. Clonidine in low doses have shown to prolong sensory blockade and has prolonged postoperative analgesia for Gynecological surgeries, knee arthroscopies and ambulatory inguinal herniorrhaphy.

Higher doses of clonidine have reported to cause hypotension andmarked sedation. So we choose low dose of intrathecal clonidine. Systemic, epidural administration of clonidine produces sedation, a central effect of α_2 adrenergic receptors noted in the dose range of 150-450µg and in our study it was not observed in Group BC due to use of low dose of clonidine.

Neostigmine produced analgesia depends on the release of NO in the spinal cord and also by increasing acetylcholine in the spinal synapses which leads to prolonged stimulation of nicotinic and muscarinic receptors. Dose of Neostigmine is selected based on the previous studies which showed that low doses of neostigmine intrathecally produced prolonged postoperative analgesia without side effects. The overall results of our study correlates with studies by Hye Ma [8] who declared that intrathecal neostigmine was associated with less haemodynamic fluctuations. Incidence of nausea and vomitings is less in both groups.

Hence in the present study, we noticed that onset for sensory blockade was hastened with addition of neostigmine. We also noted that duration of analgesia was prolonged with addition of clonidine compared to neostigmine. This correlates with the study by Yoganarasimha et al. [9].

In present study, the mean time for motor block onset and the mean time taken for maximum motor blockade was significantly faster in neostigmine group than compared to group BC [10]. Neostigmine produces nausea and vomitings and this was observed in our study also, 7 patients out of 25 had PONV which can be explained due to rostral spread of drug to brainstem [11]. Bradycardia was seen in 30% of neostigmine group 7-10 min after injection of drug, with a mean heart rate of 52-58. Bradycardia with clonidine is seen around 20-30 min after injection of drug. All the pts responded well to Atropine 0.6mg. Sedation scores for BC group [4] is higher than BN group [2].Time for rescue analgesic is prolonged in both groups andit is more in Clonidine group.

Conclusion

The use of intrathecal neostigmine 50 µg added to 12.5 mg hyperbaric bupivacaine significantly hastens the onset of sensory and motor block when compared to 75 µg clonidine. Clonidine prolongs duration of analgesia more than neostigmine, but is associated with hypotension,which can be easily managed with vasopressors.

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