

## A Comparative Evaluation of Calcitonin, Dexmedetomidine and Fentanyl Used as Adjuvants to 0.5% Hyperbaric Bupivacaine In Spinal Anaesthesia for Lower Limb Surgeries

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### Abstract

The present study was undertaken in GMC Jammu to compare the efficacy and safety of calcitonin, dexmedetomidine and fentanyl used as adjuvant to bupivacaine in spinal anaesthesia. 120 patients (ASA class I and II) aged 18 to 60 years, scheduled to undergo lower limb surgeries were included in this prospective, randomized trial. The patients were randomly assigned to one of the following four groups of 30 each: Group 1: Control (B) Group received 2.5 ml of 0.5% bupivacaine & 1 ml of normal saline. Group 2: Bupivacaine Calcitonin (BC) Group received 2.5 ml of 0.5% bupivacaine & 1ml (100IU) of calcitonin. Group 3: Bupivacaine Dexmedetomidine (BD) Group received 2.5 ml of 0.5% bupivacaine & 5microg of dexmedetomidine in 1 ml of normal saline. Group 4: Bupivacaine Fentanyl (BF) Group received 2.5 ml of 0.5% bupivacaine & 25microg of fentanyl in 1ml of normal saline. The result of the study showed statistically significant prolongation of sensory and motor block, decreased analgesic requirement, with minimal side effects with dexmedetomidine. Calcitonin resulted in prolongation of sensory block but it was associated with few side effects. Fentanyl showed least prolongation of sensory effects.

### Key words

Calcitonin, Dexmedetomidine, Fentanyl, Bupivacaine, Spinal Anaesthesia

### Introduction

Since the onset of spinal anaesthesia many agents are being used as adjuvants to bupivacaine to increase the length and depth of anaesthesia. Although endogenous opioid system is the main modality of pain perception, other endogenous neurochemical systems may also play a role in analgesia. Presence of opioid receptors in dorsal horn of spinal cord was the basis of spinal and epidural administration of opioids in the treatment of pain (1). Such methods of administration of anaesthetics may induce severe side effects including respiratory depression (2). Therefore, attempts should be made to add various agents with local anaesthetics so as to result in more effective and prolonged analgesia with minimal complications. With the discovery of non opioid analgesics system, calcitonin (sCT) which acts on this system, has enough potential for clinical usefulness to warrant its study. It is a polypeptide

hormone which is extensively found in CNS system(3) and is involved in calcium and phosphorus metabolism(4). Human studies have used salmon calcitonin (sCT) in the management of chronic pain associated with bone diseases (5) or bone cancer (6) by various routes of administration and by subcutaneous administration in acute postoperative pain not related to bone diseases (7).

Dexmedetomidine, a new highly selective  $\alpha_2$  agonist is under evaluation as neuroaxial adjuvant since it provides stable hemodynamic condition, good quality intraoperative and prolonged postoperative analgesia with minimal side effects (8, 9). Dexmedetomidine has been approved by FDA as a short term sedative for mechanical ventilation in ICU patients. So far no study has been carried out comparing these agents (dexmedetomidine, calcitonin

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,fentanyl) with hyperbaric bupivacaine . Therefore, we undertook this study to see their effects upon Indian population.

### Materials and Methods

After obtaining approval from Hospital Ethical Committee, the study was undertaken in the Department of Anesthesiology and Intensive Care, Government Medical Collage, Jammu. Written consent was obtained preoperatively from the patients/attendants. 120 ASA I-II patients of either sex, between the age group of 18-60 years scheduled for lower limb surgeries were included in the study. Exclusion criteria included:

- Patients using adrenergic receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors.
- Patients with cardiac dysarrhythmias.
- Body weight >120 kg or height <150 cm.
- Pregnant patients.
- Alcoholics and drug addicts.
- Patients having positive hypersensitivity skin test with calcitonin.
- Patients with contraindications for spinal anesthesia.

A preanesthetic check-up was done prior to surgery. Routine investigations were done. Special investigations if needed were advised. Overnight sedation was given with tablet alprazolam 0.25mg. Patients were kept fasting for 8 hours prior to surgery.

Patients were randomly allotted into the following groups: Group 1: Control (B) Group received 2.5 ml of 0.5% bupivacaine & 1 ml of normal saline.

Group 2: Bupivacaine Calcitonin (BC) Group received 2.5 ml of 0.5% bupivacaine & 1ml (100IU) of calcitonin.

Group 3: Bupivacaine Dexmedetomidine (BD) Group received 2.5 ml of 0.5% bupivacaine & 5microg of dexmedetomidine in 1 ml of normal saline.

Group 4: Bupivacaine Fentanyl (BF) Group received 2.5 ml of 0.5% bupivacaine & 25microg of fentanyl in 1ml of normal saline. 18G intravenous cannula was inserted and ringer lactate infusion was started 30 minutes before surgery. In patients of group 2 i.e. bupivacaine calcitonin (BC) group, subcutaneous infiltration of calcitonin was done to look for an immune response to protein antigen before injecting it in the intrathecal space. It was performed in the following way:

A dilution of 10IU/ml was prepared by withdrawing 0.1 ml of drug into an insulin/tuberculin syringe. The syringe was filled upto 1ml with 0.9% normal saline. 0.1ml was injected intracutaneously on the inner forearm. The injection site was observed for 15 min after the injection for the appearance of more than mild erythema (>5mm) or wheal. In the operation room, monitoring was

established with ECG, pulse oximetry and non-invasive blood pressure. The intrathecal anaesthetic adjuvant solution was prepared prior to performing spinal injection. All solutions were prepared under aseptic technique, using normal saline where reconstitution and dilution was required. 1 ml of adjuvant solution containing the specified dose of drug was mixed with 2.5 ml of 0.5% heavy bupivacaine. Under all aseptic precautions, the skin and interspinous ligament over the L3-L4 interspace was infiltrated with 2ml of 1% lidocaine. Lumber puncture was then performed in the sitting position at L3-L4 level through midline approach using a 25 gauge Quincke spinal needle. On recognizing free flow of CSF, the intrathecal anaesthetic adjuvant solution was injected over 15-20 seconds, aspirating CSF at the beginning and end of the injection, to confirm needle position. Thereafter, patients were placed in the supine position for surgery. The position of the table was kept horizontal. Heart rate (HR), non-invasive blood pressure (NIBP) and oxygen saturation (SPO2) were monitored and recorded every 5 minutes after the block for half an hour then every 10 minutes until the end of surgery. Time calculation was started considering the time of intrathecal injection as zero. The sensory level was assessed by loss of pinprick sensation using a blunt 25G needle every 2 minutes for the first 20 minutes. The peak sensory level and the time to reach peak sensory level were recorded before surgery. Thereafter, the sensory level was checked after every 10 minutes till the point of 2 segment regression level was observed.

The motor level was assessed according to the modified bromage scale.

*Bromage 0:* The patient is able to move the hip, knee and ankle.

*Bromage 1:* The patient is unable to move the hip, but is able to move the knee and ankle.

*Bromage 2:* The patient is unable to move the hip and the knee, but is able to move the ankle.

*Bromage 3:* The patient is unable to move the hip, knee and ankle. Time to reach bromage 3 motor block was also recorded before surgery.

Sedation was assessed according to the following sedation score:

*Modified Ramsay Sedation Score:*

1. Anxious and agitated or restless, or both.
2. Co-operative, oriented and tranquil.
3. Drowsy, but responds to commands.
4. Asleep, brisk response to light glabellar tap or loud auditory stimulus.
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus.
6. Asleep and unarousable.

The incidence of adverse effects such as nausea, vomiting, pruritus, respiratory depression, hypotension, arrhythmias, and restlessness were recorded. Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or fall below 90mm Hg, was treated with intravenous mephtermin in increments of 3 mg & intravenous fluid. Bradycardia, defined as heart rate <50 beats per minute, was treated with intravenous atropine in increments of 0.3-0.6 mg. Oxygen (2 liters/minute) was administered via a mask, if oxygen saturation fell below 90%. Restlessness was treated with intravenous midazolam in increments of 1

mg after the block. Nausea and vomiting was treated by intravenous granisetron 1 mg.

Postoperatively; sensory level, bromage score, sedation score and pain score were recorded every 30 minutes in the recovery room. The time from intrathecal injection to sensory regression to S1 dermatome and motor block regression to modified bromage O were recorded. Pain score were recorded by using Visual Analogus Score between 0 to 10 till the first dose of rescue analgesia. Intravenous infusion of Diclofenac 75 mg was given as rescue analgesia when VAS was ?

	<b>Group B (n=30)</b>	<b>Group BC (n=30)</b>	<b>Group BD (n=30)</b>	<b>Group BF (n=30)</b>	<b>p value</b>
Age (years)	39.67±12.33	40.84±9.79	39.94±11.42	41.5±9.78	>0.05
Sex(M:F)	04:01	03.28:01	05:01	04:01	>0.05
Height (cm)	167.97±5.38	169.8±6.56	167.47±6.35	169.76±6.18	>0.05
Weight (kg)	69.1±7.22	70±7.71	71.44±8.56	70.33±7.11	>0.05
Duration of Surgery (min)	115±22.40	121±15.39	114±22.06	119.34±19.98	>0.05

	<b>Group B (n=30)</b>	<b>Group BC (n=30)</b>	<b>Group BD (n=30)</b>	<b>Group BF (n=30)</b>	<b>p value</b>
Highest sensory level	T6-T10	T7-T10	T7-T10	T6-T10	>0.05
Time from injection to highest sensory level( min)	10.53±2.34	10.86±2.66	10.40±3.25	11.40±3.11	>0.05
Time of two segment regression from the highest sensory level(min)	79±12.13	134±11.91	148.33±15.55	88±13.99	0.00
Time of sensory regression to S1 from highest sensory level (min)	152±22.19	254±35.87	335±57.93	181±25.5	0.00
Time to rescue analgesia (min)	168±30.10	283±44.34	353.66±53.20	199±20.06	0.00
Onset to Bromage 3 (min) motor Block	9.8±3.03	10.20±3.87	8.60±4.33	9.86±2.40	0.31
Regression to Bromage 0 (min)	129±26.30	131±20.06	306.90±57.68	138±33.05	0.00

*Values given in mean ± SD.*

4. Patients were also observed for vitals and hemodynamic parameters throughout the postoperative period. Analysis was done using computer software MS Excel and SPSS version 12.0 for windows. Outcome measures were presented as percentage for qualitative variables and mean  $\pm$  SD for quantitative variables. Baseline comparability was ensured and its significance evaluated by chi square test/t test/ANOVA. One way ANOVA was employed to find statistical significance among groups which was followed by Bonferroni t test to evaluate intergroup significance. All p values reported were two tailed and p value of  $< 0.05$  was considered as statistically significant unless specified otherwise.

**Result**

All patients (n = 120) completed the study; there was no statistical difference in patients' demographics or the duration of surgery as shown in Table 1. The mean values of mean arterial blood pressure, heart rate and oxygen saturation were comparable among the 4 groups (Fig 1&2).

No statistical significance was seen in the highest level of sensory block achieved, time to reach the highest level of sensory blockade and the onset time of modified Bromage 3 motor block amongst the groups. (Table 2)

The regression time to reach modified Bromage 0 in Group BD was significantly longer than that for group B, group BC and group BF, with no significant difference between group B, BC and BF. 2 segmental regression of sensory block to S1 and time of giving of rescue analgesia were longest in group BD followed by group BC, then group BF and least in group B. This difference was highly significant between group B and group BC, group B and

group BD, group BD and group BC, group BC and group BF, group BD and group BF. However, the difference between groups B and BF was significant. Side effects of spinal block are shown in Table 3. The overall side effects were more in group BC followed by group BF then in group B and least of all in group BD.

Hypotension was seen in 4 patients in group BF, 3 patients in group B and 2 patients in group BD. None of the patients in group BC developed hypotension. These patients responded well to fluid bolus and iv mephtermin 2 patients in group B and 1 in group BF developed bradycardia. However, it was easily managed with atropine. Nausea and vomiting were most in group BC (8 patients) followed by group B and BF (2 patients Each) and least in group BD (only 1 patient).

The sedation score was between 1 and 2 in all groups. Shivering was experienced by 6 patients in group BC followed by 3 patients each in group B and BF and only 1 patient in group BD. Pain abdomen and restlessness was seen in 5 and 3 patients respectively in group BC only. Restless patients responded well to increments of 1 mg of injection midazolam

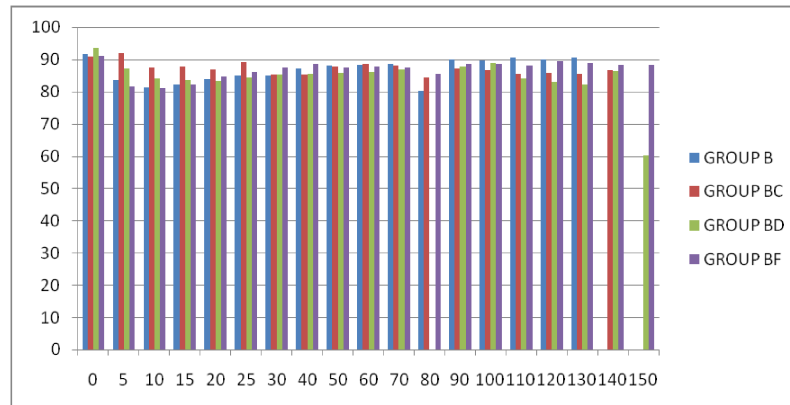
None of the patients got desaturated. Pruritis was absent in all the groups except in group BF, in which 5 patients developed pruritis.

**Discussion**

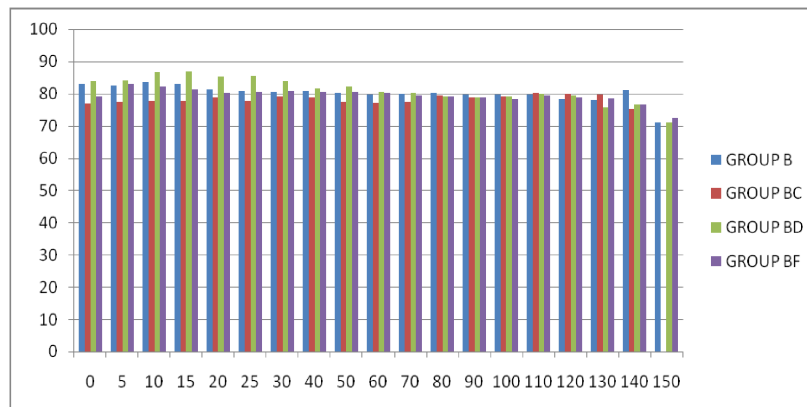
Dexmedetomidine is an alpha 2 adrenergic agonist which has about ten times higher affinity for  $\alpha_2$  receptors than clonidine (12) (Kanazi *et al*, 2006). It is believed that dexmedetomidine produces its analgesic effect by inhibiting the release of c-fibre transmitters and by postsynaptic dorsal horn neurons (13) (Yaksh TL *et*

<b>Table 3: Incidence of Side effects</b>				
	<b>Group B (n=30)</b>	<b>Group BC (n=30)</b>	<b>Group BD (n=30)</b>	<b>Group BF (n=30)</b>
Nausea and Vomiting	2	8	1	2
Hypotension	3	0	2	4
Bradycardia	2	0	0	1
Desaturation	0	0	0	0
Pruritus	0	0	0	5
Shivering	3	6	1	3
Sedation	0	0	1	0
Pain Abdomen	0	5	0	0
Restlessness	0	3	0	0

**Fig 1. Intraoperative Mean Arterial Pressure (MAP)**



**Fig 2. Intraoperative Heart Rate (Beats per minute)**



al, 1981). Its prolongation of motor effects may be due to inhibition of excitatory amino acid released from spinal interneurons. This study shows significant prolongation of the duration of analgesia with dexmedetomidine as an adjuvant to hyperbaric bupivacaine. The patients in this group had prolonged motor and sensory block, remained hemodynamically stable, had minimal side effects with reduced postoperative pain score compared to control. This is in concordance with the study of Gupta R *et al*, 2011(14) and Al-Ghanam *et al*, 2009 (8) who reported a significant prolongation of sensory and motor block with dexmedetomidine/bupivacaine group in comparison to fentanyl/bupivacaine group. Gupta R *et al*, 2011 reported prolongation of time of analgesia with dexmedetomidine group as compared to fentanyl group. Mohamed AA *et al*, 2012(9) also reported longer analgesia with intrathecal dexmedetomidine in comparison to control group.

Shukla *et al*, 2011(13); Kanazi GE *et al*, 2006(12); Al Mustafa *et al*, 2009 (15) found no significant hemodynamic effects of addition of dexmedetomidine to

intrathecal bupivacaine when compared to their respective control groups. Eisenach *et al*, 1996 (16) concluded that the cause of sedation after intrathecal dexmedetomidine may be related to its systemic absorption and vascular redistribution to higher centers or cephalad migration in CSF. But we did not find significant sedation after addition of intrathecal dexmedetomidine in our study. This could be attributed to the small dose of dexmedetomidine used by us.

Calcitonin is a non opoid endogenous analgesic which has enough potential for clinical usefulness to warrant its use as adjuvant. It is involved in calcium and phosphorous metabolism. Calcitonin causes an increase of plasma  $\beta$ -endorphin level acting at the hypothalamus and pituitary level, either directly or indirectly through monoaminergic neurotransmitters (Kyviaki Mystakidou *et al*, 1999(17)). Prolonged analgesia in animals and humans has e.g. been observed after intrathecal administration of calcitonin(18,19). Since calcitonin induces analgesia not modified by opoid antagonists, a non opoids analgesic pathway could be involved although exact mechanism still remains to be

identified. In the current study we found that calcitonin significantly prolongs the analgesic effects but it has side effects like nausea and vomiting (26%), pain abdomen (16%), restlessness (10%) and shivering (20%) which increases patients discomfort. These could be attributed to hypocalcemia caused by calcitonin.

Moraby M *et al*, 2007(20) observed that the patients of calcitonin group had the longest duration of pain relief in his study, followed by patients in fentanyl group and shortest duration of pain relief was observed in the control group. This is in agreement with our study. However, he reported incidence of side effects like nausea and vomiting (6.6%), restlessness (30%), pain abdomen (3.3%) and shivering (5%). Miralles *et al*, 1987(4) in his study with intrathecal calcitonin group reported less pain upto 6 hours of surgery in calcitonin group in comparison to control group with 6.6% patients having nausea and vomiting. Blanchard *et al*, 1990 (22) observed vomiting in 78% of patient receiving intrathecal calcitonin. Fentanyl is an opioid used with bupivacaine. There was significant difference in the length and depth of spinal anaesthesia as compared to control but with side effects. Bhure *et al*, 2011(23) also found that the analgesia was prolonged after fentanyl in comparison to intrathecal control group. Bhure *et al*, 2011(23) observed nausea and vomiting in fentanyl (6.7%) and control (10%) group which was not significant statistically. Dayioglu *et al*, 2009(24) in their studies with fentanyl did not find respiratory depression as a possible side effect. Biswas *et al*, 2002(25); Bhure *et al*, 2011(23) also reported hemodynamic comparability after addition of fentanyl to intrathecal bupivacaine in comparison to their respective control group as is with our study. Our study was useful in the sense that the three adjuvants were compared which has never been done before. We found that dexmedetomidine was a dependent agent, prolonging the depth and length of analgesia in spinal anaesthesia. Fentanyl lengthen the analgesic effect but had a shorter duration where as calcitonin did prolonged the effect of local anaesthetics what was associated with manageable side effects. We concluded dexmedetomidine is best agent of all three used as adjuvants to bupivacaine in spinal anaesthesia.

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