

Comparative Study Of Subarachnoid Calcitonin And Fentanyl As Adjuvant With Local Analgesic Bupivacaine For Postoperative Pain Relief: A Double Blind Study

M Moraby, A Tiwari, S Jaiswal, N Tewari, V Rastogi

Citation

M Moraby, A Tiwari, S Jaiswal, N Tewari, V Rastogi. *Comparative Study Of Subarachnoid Calcitonin And Fentanyl As Adjuvant With Local Analgesic Bupivacaine For Postoperative Pain Relief: A Double Blind Study*. The Internet Journal of Anesthesiology. 2006 Volume 13 Number 1.

Abstract

Background: The study was aimed to compare effect of subarachnoid calcitonin and fentanyl as adjuvant with bupivacaine for postoperative pain relief and establishing the analgesic effect of calcitonin after subarachnoid administration in acute postoperative pain.

Materials and Methods: In a prospective, double blinded, randomized sequential allocated study, 60 ASA I and II physical status patients were divided in three groups of 20 each

Group A received 3 ml of bupivacaine (15 mg) with 100 i.v. calcitonin, group B received 3 ml bupivacaine with 25 µg fentanyl and group C received 3 ml of bupivacaine with 1 ml saline as control.

Results and conclusion: Addition of calcitonin as adjuvant in the subarachnoid enhances intraoperative condition with no adverse effects on hemodynamic stability, quality of sensory and motor block. However, intrathecal administration of calcitonin produces analgesic effect and appears to provide > 3 hrs of additional analgesia over heavy bupivacaine above and > 1 ½ hr over fentanyl. Its most disturbing adverse effect was vomiting, nausea and restlessness / nervousness.

INTRODUCTION

Spinal Anesthesia has enjoyed a long history of success and recently, celebrated a centennial anniversary. Recent trends of spinal anesthesia are towards addition of adjuvants like opioid, ketamine, clonidine, neostigmine, midazolam etc to local anesthetic to increase efficacy, duration and to maintain analgesia far into the postoperative period. Hamber et al (1999)

The results of advances in newer drugs, monitoring equipment, and a greater understanding of the relationships between the doses, concentrations and their subsequent effect, subarachnoid blockade with local anesthetics in surgeries below the umbilicus and lower limbs is of common practice. Bupivacaine is a local anesthetic and is being used as control in this study.

Advances in the understanding of the pathways for pain transmissions have allowed the introduction of new methods for the treatment of acute and chronic pain. Although the

endogenous opioid remains the main modulator of pain perception, other endogenous neurochemical systems may also play a role in analgesia. The finding of opioid receptors in the dorsal horn of the spinal cord was the basis for the subarachnoid administration of opioid in the treatment of pain. It is also postulated that the non-opioid endogenous analgesics system and neurotransmitters release may have a role in the modulation of pain.

Fentanyl is perhaps the best studied and most commonly used lipophilic opiate use for intrathecal analgesia. It has a rapid onset of action with a short duration of action and provides a better quality of surgical block. However, its use is not totally devoid of significant adverse effects such as pruritus, nausea, vomiting, sedation, respiratory depression and urinary retention. Belzarena et al (1992), Reuben et al (1994), Ben David et al (1997)

Calcitonin, a natural hormone has been demonstrated to relieve pain independently of its peripheral action on bone

and an increase of plasma Beta-endorphins level acting at the hypothalamus and at/or the pituitary level, either directly or indirectly through monoaminergic neurotransmitters have shown to have analgesic effect. Kalle et al (1999)

This study is undertaken to compare the effect of subarachnoid calcitonin and fentanyl as adjuvant with local analgesic bupivacaine for postoperative pain relief and to establish the analgesic effect of calcitonin after subarachnoid administration in acute postoperative pain.

MATERIAL AND METHODS

This study was conducted in the Department of Anesthesiology and Intensive Care, Sir Sunderlal Hospital, Banaras Hindu University. Prior to commencing the investigation, approval was obtained from both the ethical and hospital research committee.

Participants in this study were explained of the anesthetic procedure and informed consent was taken. 60 ASA I & II physical status patients undergoing surgery below the umbilicus and lower extremities, including orthopedics, urology, gynecological surgery and general surgery lasting less than 3 hrs were enrolled into this prospective, double-blinded, randomized sequential allocation study.

Exclusion criteria from the study were -

Patient refusal, ASA III & IV, Hypovolaemia, Bleeding diathesis and coagulopathy, Sepsis, Valvular heart disease, Pregnant patient, Raised intracranial pressure, Local skin infection at spinal level L₁-S₁, Any other neurological disorders of the extremities or deformity of spines.

All participants were premedicated with oral Alprazolam 0.5 mg on eve of surgery and 2 hrs prior to morning surgery with few sips of water.

They were allocated randomly into three groups according to the drug used

Group A: Patient receiving subarachnoid block with 0.5% heavy bupivacaine 3ml with 1 ml calcitonin (100 I.U).

Group B: Patient receiving subarachnoid block with 0.5% heavy bupivacaine 3 ml with 1 ml of 25 mcg of fentanyl (diluted with normal saline)

Group C: Control group / placebo- patient given subarachnoid block with 0.5% heavy bupivacaine 3 ml with 1 ml of normal saline

Participants were randomly allocated to one of control, fentanyl or salmon calcitonin groups using a sealed envelope technique.

The intrathecal adjuvant solutions were prepared prior to performing the spinal injection by a separate resident anesthetist who had no further involvement with the patient. All solution was prepared under strict aseptic technique using 0.9% normal saline where reconstitution and dilution required. Once prepared all solution were deposited into is sterile heavy which was labeled with the trial number. The labeled solution was presented in a 2 ml syringe out of which 1 ml was added to a 3 ml solution of 0.5% heavy bupivacaine. Thus the anesthetist who managed the case was unaware of which solution had been administered. In the operation theatre, patient inquired for 8 hrs fasting period and was asked to void the bladder.

After infiltrating the skin and interspinous ligament over the L₃₋₄ interspace with 1% lidocaine 2ml, the subarachnoid space was entered using a 25-gauge pencil point spinal needle. Once free flow of CSF has been recognized from all four quadrants, the intrathecal anesthetic solution was injected over 20 seconds, aspirating CSF at the beginning and end of the injection to confirm needle position. On completion of spinal injection, all patients were monitored for the following-

Heart rate, NIBP, The level of sensory and motor block using Bromage score

The duration of surgery in all 3 groups were noted and time to requirement of first dose of analgesia noted by Visual Analogue Scale (VAS) of 0-10 cm (with 0= no pain and 10= severe pain). A slide rule marker was used at regular interval of postoperative visit to assess the level of pain.

Finally the impression of the patient was asked after one day of surgery.

STATISTICAL ANALYSIS

The observation in various groups was compared statistically using student 't' test and analyzed by SPSS software.

OBSERVATIONS AND RESULTS

This study was conducted on sixty patients of either sex of ASA grade I or II scheduled for elective surgery below the umbilicus. The patients were allocated in three groups (A, B and C) comprising of twenty (n=20) patients each. Group A received subarachnoid block with 0.5% heavy bupivacaine

with 100 I.U. Salmon calcitonin. Group B received subarachnoid block with 0.5% heavy bupivacaine with 25 g fentanyl. Group C received subarachnoid block using 0.5% heavy bupivacaine, alone which served as control.

The patients demographic data were observed for heart rate, mean blood pressure, oxygen saturation, duration of surgery, objective and subjective pain relief and complications including nausea and vomiting, respiratory distress, restlessness, hypotension, pruritus and sedation.

Figure 1

Table 1: Distribution of patient according to age and in comparison with each group

Group	Age (years) (Mean \pm SD)	M:F Ratio	Duration of surgery Min (Mean \pm SD)
Group A (n=20)	43.15 \pm 12.75	9:11	92.6 \pm 38.53
Group B (n=20)	41.40 \pm 13.13	7:13	75.15 \pm 24.28
Group C (n=20)	43.10 \pm 11.23	6:14	86.05 \pm 27.54

There was no significant difference ($p > 0.05$) observe in mean age, male: female ratio and duration of surgery among the different groups.

Figure 2

Table 2: Distribution of patient according to height of spinal block achieved in each group at time of start of operation

Level of spinal block achieved	Group			Total	%
	A	B	C		
T ₄	14	11	11	36	60%
T ₅	-	4	7	11	18.33%
T ₆	4	4	2	10	16.66%
T ₇	-	-	-	-	-
T ₈	2	1	-	3	5%

The level of sensory block achieved in each group at the time of start of operation checked by pinprick method. As shown in table:2 ,the overall level of sensory block achieved in all three groups were comparable ($p > 0.05$) with more than 60% at T₄ and 95% above T₆ which was sufficient for surgeries below the umbilicus as no patient required supplement of analgesia during the perioperative period. The analgesia is related to the extent of the spinal blockade.

The mean heart rate, mean arterial blood pressure, mean oxygen saturation (as measured by pulse oximeter) was measured at baseline, 5 minutes after subarachnoid block, then every fifteen minutes up to 75 minutes .On comparing, the above parameters among each group, no significant

difference ($p > 0.05$) was observed at different intervals of time in minutes during the whole surgical procedure.

THE QUALITY OF MOTOR BLOCKS

The quality of motor blocks achieved was assessed by a Bromage score .It was observed that in all three groups A, B and C, patients had a complete motor block.

THE QUALITY OF ANESTHESIA

The quality of intraoperative surgical anesthesia was assessed by a three point scoring system. In all three groups A, B and C, the quality of surgical anesthesia was judged as excellent with no sensation at all.

Figure 3

Table 3: Distribution and in comparison with each group to first dose of analgesia required

Group	Time of first dose of analgesia (minute) (Mean \pm SD)
Group A (n=20)	323.00 \pm 163.38
Group B (n=20)	202.40 \pm 64.40
Group C (n=20)	168.55 \pm 23.65

Group Comparison

Group	't' value	'p' value
Group A vs Group B	3.071	0.004 (HS)
Group A vs Group C	4.184	0.000 (HS)
Group B vs Group C	2.206	0.033 (S)

The duration of pain relief in minutes observed at VAS 4/5 in group was A – 323 163.38, group B – 202.40 64.40 and group C – 168.55 23.65. The longest duration of pain relief was observed in group A (mean=323 minutes) as compared to group B (mean=202.4 minutes) and group C (mean=168.55 minutes). The pain relief was statistically highly significant ($p = 0.004$ and $p = 0.000$) as compared with group B and group C respectively. However, in group B comparison with group C showed a just significant change ($p = 0.033$). Thus group A had longest mean duration of analgesia as compared to group B and group C.

Figure 4

Table 4: Distribution of patient according to adverse effect

	Group A		Group B		Group C	
	No	%	No.	%	No	%
No untoward side effect	8	40%	7	35%	8	40%
Hypotension	5	25%	4	20%	7	35%
Hypoxia	2	10%	4	20%	3	15%
Vomiting and nausea	6	30%	2	10%	1	5%
Restlessness	6	30%	1	5%	-	-
Shivering	1	5%	2	10%	1	5%
Urinary retention	1	5%	1	5%	0	-
Pruritus	0	-	4	20%	0	-
Sedation	0	-	4	20%	0	-

COMPLICATIONS

The incidence of complications in various groups is shown in Table 4. Five (25%) cases in group A had hypotension as compared to 4 (20%) in group B and 7(35%) in group C. The incidence of hypotension in group C was statistically significant ($p<0.05$) as compared to group A and B. However there is insignificant difference in the incidence of group A as compared to group B ($p>0.05$).

The incidence of respiratory depression was 2(10%) in group A as compared to 4(20%) in group B and 3(15%) in group C. This signifies that there was significant difference between group A as compared to group B ($p<0.05$) and statistically insignificant between group A and group C.

Nausea and vomiting occurred in 6(30%) patients in group A as compared to 2(10%) in group B and 1(5%) in group C. The incidence of nausea and vomiting was highly significant $p<0.05$ in group A as compared to both group B and C.

Restlessness/ nervousness occurred in 6(30%) patients in group A versus one in group B and none having this complication in group C. Restlessness was relieved with injection of midazolam 1-2mg i.v. This was highly significant $p<0.05$.

Shivering occurred in one (5%) in group A as compared to 2(10%) in group B and one (5%) in group C. The incidence of shivering was statistically insignificant ($p>0.05$) in between all three groups.

Urinary retention occurred in one (5%) in group A and one

(5%) in group B but none was observed in group C. On comparing incidence of urinary retention between group A, B and C showed no significant difference ($p>0.05$).

Pruritus and sedation occurred in 4(20%) patients of group B not observed in either group A or group C, which was highly significant $p<0.05$. Pruritus and sedation was self-limiting, as patients did not require any medical intervention.

DISCUSSION

This study was undertaken to investigate the analgesic effect of salmon calcitonin in the subarachnoid space and to compare it with fentanyl in 0.5% heavy bupivacaine.

In this study, on comparing the demographic data between group A, B and C that included age, weight, height and sex of participants showed statistically insignificant (p value > 0.05) difference.

During the intraoperative surgical procedure, the cardiovascular stability was assessed by pulse rate and mean arterial pressure and was compared with all groups A, B and C. No significant difference ($P>0.05$) in pulse rate, mean arterial pressure and oxygen saturation in either of the three groups at baseline, 5, 15, 30, 45, 60 and 75 min intervals was observed.

The level of sensory block achieved after the subarachnoid block in all the three groups were deemed adequate with no untoward complaint of pain from patients during the intraoperative period. Sensory block were 95% at T₆ level dermatomes at the time of starting the surgical procedure.

The quality of motor blocks achieved was assessed by a Bromage score with 1 = complete motor block, 2 = unable to flex the knee but can flex the ankle articulation, 3 = unable to perform the leg raise test but can flex the leg on the knee articulation and 4 = No motor block at all. It was noted that in all 3 groups. Patient had a complete motor block.

The quality of intraoperative surgical anesthesia was assessed by a three point scoring system with 1 = Excellent, no sensation at all; 2 = adequate with no extra analgesia required and 3 = discomfort analgesia required. In all three groups, the quality of surgical anesthesia was judged as excellent with no sensation at all.

The duration of surgery in group A, B, C had a mean value of 92.60 ± 38.63 ; B = 75.15 ± 24.27 and C = 86.05 ± 27.53 and was statistically insignificant $P> 0.05$.

The time to while the patient required the first dose of analgesia, as assessed by the VAS scale was- calcitonin group mean 323.00 ± 163.83 , fentanyl 202.40 ± 64.40 and plain bupivacaine 168.55 ± 23.65 with a respective p value of 0.004 with calcitonin Vs fentanyl, calcitonin vs bupivacaine $p < 0.000$ and fentanyl vs bupivacaine $p < 0.033$. Comparatively, calcitonin showed a significant duration of analgesia in postoperative period compared to fentanyl and plain bupivacaine. It was also observed that patients who had received salmon calcitonin and who had bone surgeries or malignancy had longer pain relief postoperatively compared with other surgeries. Lyritis et al (2002)

Miralles et al (1987) in a randomized double blind study found that in all instances ranging from 3 to 72 hrs post surgery, the salmon calcitonin treated patients had significantly less postoperative pain. Also, the requests for analgesics were significantly lower or absent in the salmon calcitonin treated group. The study also showed that the greatest level of pain occurred at 6 hrs after surgery in the control group my study showed that the requirement for first dose of analgesia was around a mean of $5^{1/2}$ hrs.

Fraioli et al (1982) administered 1.5 mg/kg body weight of pure synthetic salmon calcitonin in lumbar subarachnoid space in patient with chronic intractable of terminal cancer patient and showed that all patient had considerable amelioration of pain. This, probably, suggesting why in the present study patients with malignancy had considerably less pain in post operative period. Kalle et al (1999), Martinez et al (2003)

Fraudeschini R et al (1993) stated that the analgesic effect of salmon calcitonin occurs independently of its peripheral action. It has been postulated that administered calcitonin binds to its receptors located on neural elements, thereby

affecting the analgesic pathway controlling pain perception or elevating the nociceptive sensitivity threshold. Salmon calcitonin induced analgesia is mediated by activation of the endogenous opioid system and namely by increasing Beta endorphins secretion. This correlates with the findings observed in the present study.

CORRESPONDENCE TO

S.Jaiswal, M.D Department of Anesthesiology Institute of Medical Sciences Banaras Hindu University Varanasi .India
E-mail; drsushiljswl@rediffmail.com

References

1. Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small-dose dilute bupivacaine: Better anesthesia without prolonging recovery. *Anesth Analg* 1997;85:560-5
2. Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. *Anesth Analg* 1992;74:653-7
3. Fraioli F, Fabbri A, Gnessi L, Moretti C, Santoro C, Felici M. Subarachnoid injection of salmon calcitonin induces analgesia in man. *Eur J Pharmacol* 1982;78:381-2
4. Franceschini R, A Cataldi, P Cianciosi, A Garibaldi, Corsini G, Barreca T, Rolandi E. Calcitonin and -endorphin secretion. *Biomed & Pharmacother* (1993) 47: 305-309.
5. Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. *Reg Anesth Pain Med* 1999; 24:255-63
6. Kalle Varav. Continuous Subcutaneous Administration of High-Dose Salmon Calcitonin in Metastasis: Pain Control and Beta-Endorphin Plasma Levels. *Journal of Pain and Symptom Management* 1999; 18 (5): 1-2.
7. Lyritis GP, Trovas G. Analgesic effects of calcitonin. *Bone* 2002;30:71-74
8. Martinez MJ, Roque M, Alonso-Coelo P, Catala E, Carcia JL. Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev* 2003; (3): CD003223.
9. Miralles, F Lopez-Soriano, MM Puig, D Perez and F Lopez-Rodriguez. Postoperative analgesia induced by subarachnoid lidocaine plus calcitonin. *Anesthesia & Analgesia* 1987 ; 66: 615-618
10. Reuben SS, Dunn SM, Duprat KM, O'Sullivan P. An intrathecal fentanyl dose-response study in lower extremity revascularization procedures. *Anesthesiology* 1994;81:1371-5

Author Information

M. Moraby, M.D.

Junior resident, Department of Anesthesiology, Institute of Medical Sciences
Institute of Medical Sciences, Banaras Hindu University

A. Tiwari, M.D.

Senior Resident, Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University

S. Jaiswal, M.D.

Junior Resident, Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University

N. Tewari, M.Sc.

Junior Research Fellow, Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University

V. Rastogi, M.D.,D.A.

Professor and Head, Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University