

Original Research Article

Efficacy and safety of two different doses of intrathecal calcitonin, a randomized controlled study

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ABSTRACT

Background: Adjuvants play an important role in enhancing the quality of anesthesia and also in reducing the requirement of primary anesthetic and its related adverse events. Calcitonin is one such adjuvant. But there is still uncertainty regarding the appropriate dose of calcitonin to achieve maximum analgesic efficacy and safety. The current study is conducted to add to the existing evidence on the subject and was aimed to compare the efficacy and safety of two different doses of calcitonin as an adjuvant in patients undergoing spinal anesthesia.

Methods: A prospective randomized controlled double-blind trial was conducted in the Department of Anesthesiology and Intensive Care, Dhanalakshmi Srinivasan Medical College and Chennai Medical College, Trichy from Dec 2016 to Dec 2017. A total of 80 participants aged between 18 to 60 years, with ASA I and II physical status, undergoing infra-umbilical surgeries were randomly allocated to one of the 4 intervention groups. All the 4 intervention groups received 0.5% bupivacaine (H) 3ml as a primary anesthetic agent. Group I and III received 50 IU and 100 IU salmon calcitonin as an adjuvant. Group II received placebo and group IV (control) received no adjuvant. Pinprick test, Bromage scale and 10-point Visual analog scale (VAS) were used to measure the efficacy.

Results: All the study groups were comparable with respect to all baseline variables. The time interval to the first dose of analgesia was longest in 100 I.U. calcitonin group, followed by 50 I.U. calcitonin group, placebo control group. The mean duration of analgesia (in minutes) among group I (100I.U. calcitonin) was 230.00±92.39, 159.25±21.59 among group II (Placebo), 161.50±31.20 among group III (50 I.U. calcitonin) and 142.75±20.22 among group IV. Considering group IV (control group) as base line. The differences of duration of analgesia (in minutes) in group I, group II and group III with baseline value (group IV) were statistically significant (P value <0.05). Even though the proportion of subjects developing adverse events was slightly higher in 100 I.U. calcitonin groups compared to other groups, they were minor adverse events and were managed appropriately. There were no significant differences across the study groups in terms of hemodynamic stability.

Conclusions: Salmon calcitonin as adjuvant increases the duration of postoperative analgesia. Even though there is slightly higher incidence of adverse events with 100 I.U. calcitonin they are minor and the risk-benefit ratio favors calcitonin use. To make a categorical recommendation on the appropriate dose, there is further need for large-scale studies and pooled analysis.

Keywords: Calcitonin, Efficacy, Post-operative analgesia, Safety

INTRODUCTION

Over years many advances have been made in the management of acute postoperative pain but, pain after

surgery remains a serious cause of suffering. The tissue damage of surgery set up pathophysiological processes in the peripheral and central nervous systems if under managed it may become chronic. The recent trends in

practice of spinal anesthesia are towards the addition of an adjuvant to the local anesthetic agent to increase the efficacy and duration of analgesia longer into the postoperative period.¹ Adjuvants are the compounds which by themselves have undesirable side effects or low potency but help to reduce the postoperative opioid requirement which hinders early recovery.² Therefore a pressing need for advances in the agents and technique exists so as to improve analgesia efficacy.

Calcitonin a natural nonopioid polypeptide hormone found in the mammalian brain, cerebrospinal fluid, pituitary and is involved in calcium and phosphate metabolism.³⁻⁷ Salmon calcitonin has been used by various routes in the management of chronic pain associated with a bone disease or bone cancer.⁸ It has also been used as an adjuvant to local anesthetic in subarachnoid block to increase the efficacy of block, duration of postoperative analgesia and reduce postoperative analgesic requirements.⁹⁻¹¹ This study was carried out with the aim to compare and evaluate the efficacy of calcitonin in two different doses to provide postoperative analgesia and, to evaluate the side effect of intrathecal calcitonin administration.

METHODS

The study was conducted in the Department of Anesthesiology and Intensive Care, Dhanalakshmi Srinivasan Medical College and Chennai Medical College, Trichy, between Dec 2016 to Dec 2017. Prior to commencing the investigation, approval was obtained from the hospital ethical committee. In this prospective double-blind, randomized study eighty patient between 18-60 years of age, ASA I and II physical status undergoing surgery below the umbilicus and lower extremities lasting less than 3hrs were enrolled.

Exclusion criteria for the study were a patient refusal, ASA III and IV, hypovolaemia, bleeding diathesis, coagulopathy, sepsis, valvular heart disease, pregnant patient, raised intracranial pressure, local skin infection, any other neurological disorders of the extremities or deformity of spines and sensitivity to salmon calcitonin.

The patient was premedicated with tablet alprazolam 0.5mg on the night and early morning prior to the procedure. They were randomly allocated to four groups of twenty each:

- Group I: patients receiving subarachnoid block with 0.5% heavy bupivacaine (H) 3ml with ampoules A.
- Group II (placebo): patients receiving subarachnoid block with 0.5% bupivacaine (H) 3ml with ampoules B.
- Group III: patients receiving subarachnoid block with 0.5% bupivacaine (H) 3ml with ampoules C.
- Group IV (control): patients receiving subarachnoid block with 0.5% bupivacaine (H) 3ml.

Identical ampoules containing 50IU, 100IU salmon calcitonin in along with placebo were supplied with code (C, A and B). The patients received subarachnoid bupivacaine 0.5% (H) with one of the identical ampoules picked randomly, containing either placebo, calcitonin 50IU or 100IU. and, the identity of the ampoules was decoded only at the end of the study.

Patient's baseline non-invasive blood pressure, pulse rate, oxygen saturation and ECG monitoring were instituted. Intravenous access was established using an 18-gauge cannula and a fluid of 6-8ml/kg over 15mins was preloaded prior to subarachnoid block, followed by 8ml/kg/hr for 1sthr and finally maintenance infusion at rate 2ml/kg/hr (adjusted to blood loss). Patient sensitivity toward salmon calcitonin was looked for prior to intrathecal administration by skin sensitivity one hour prior to instituting the block. Under all aseptic precautions, the subarachnoid block was given in the L3-4 interspace with a 25-gauge spinal needle. Level of anesthesia was checked by pinprick method from dermatomes L2 to T4 and the highest level of sensory block achieved was noted, the motor block was assessed for both legs with four points Bromage scale. The pain was assessed by using a visual analog scale (VAS) of 0-10cm (with 0= no pain and 10= severe pain).

Patients were provided with their postoperative analgesia when their VAS levels were >4. Intraoperatively, whenever patient blood pressure fell below 20% of its mean arterial pressure Inj. Mephentermine 5mg IV. bolus was to be given. Oxygen supplementation was only started to the patient if the oxygen saturation fell below 90%. The patient's demographic data were recorded, and the patients were intraoperatively monitored for heart rate, mean arterial pressure, oxygen saturation, quality of block, and duration of surgery. Postoperatively patients were looked for the duration of analgesia which was measured from the time of institution of the subarachnoid block to the time patient when VAS score was > than 4 or the patient asked for an analgesic agent and was called as the time to the first dose of analgesia. Any adverse events occurring during the intraoperative and postoperative period up to first 24hours after the administration of calcitonin was also noted.

RESULTS

Demographic variables, duration of surgery and level of the sensory blockade is not affected by the addition of salmon calcitonin to bupivacaine and as shown in Table 1 it is comparable and non-significant between all the four groups and spinal anesthesia was adequate in all the instances. The patients in all four-group remained hemodynamically stable and as shown in Table 2 mean arterial pressure and oxygen saturation were comparable and nonsignificant ($P>0.01$). Duration of analgesia or the time interval when the first dose of analgesic was given has been shown in Table 3. In our study with the use of

100IU salmon calcitonin the duration of analgesia following subarachnoid block was 230±92.39minutes.

Table 1: Demographic parameters.

	Group I	Group II	Group III	Group IV	P value
Age	47.32 ± 7.86	46.70 ± 6.01	46.25 ± 6.69	46.2±5.97	0.959
Sex (m/f)	10/10	12/8	11/9	12/8	0.906
Height	147.00±8.26	150.75±5.63	149.56±6.88	150.8±5.26	0.235
Weight	60.95±6.22	61.50±6.34	61.35±7.09	62.40±5.13	0.901
Duration of surgery	96.75±20.27	83.25±22.37	92.00±21.48	97.25±24.35	0.171
Level of sensory blockade (no. of patients)	T4	9 (45%)	10 (50%)	14 (70%)	12 (60%)
	T5	8 (40%)	9 (45%)	6 (30%)	8 (40%)
	T6	3 (15%)	1 (5%)	-	-

Table 2: Showing comparison of mean arterial pressure and oxygen saturation (%).

	Group I		Group II		Group III		Group IV	
	MAP	SPO2	MAP	SPO2	MAP	SPO2	MAP	SPO2
Baseline	90.36±25.35	97.19±1.68	90.10±4.97	97.28±1.98	89.57±5.48	97.23±1.65	89.62±5.29	97.89±2.07
2 min	89.95±6.15	97.83±2.15	90.10±3.90	97.41±1.87	89.25±4.66	97.63±1.29	89.15±4.78	97.36±2.03
5 min	88.45±6.41	96.55±2.89	87.90±4.20	97.34±1.76	87.45±4.66	97.15±2.88	87.70±6.88	96.69±2.45
10 min	88.85±6.95	97.58±1.59	87.80±5.99	97.11±1.42	87.10±3.94	97.05±1.87	88.75±5.72	97.81±2.02
15 min	88.15±6.25	97.22±1.48	87.10±4.40	97.86±2.14	87.30±6.64	97.58±1.77	88.35±6.59	97.26±1.83
30 min	89.35±5.47	96.23±2.53	88.75±3.61	96.58±2.58	88.20±5.38	97.63±2.08	89.45±5.67	97.66±2.39
45 min	89.25±5.10	97.21±1.57	88.95±4.89	97.86±2.46	88.50±5.02	97.31±2.19	89.55±4.88	97.08±2.11
60 min	89.60±5.18	96.27±1.66	88.10±4.63	96.37±1.87	87.90±5.75	96.54±2.05	88.85±5.59	97.01±2.55
75 min	88.65±5.34	97.1±2.01	88.6±4.33	97.13±2.23	87.6±5.43	97.6±2.01	88.56±3.99	97.12±2.09
90 min	89.3±4.22	96.8±1.64	89.2±3.22	97.36±2.03	88.4±4.34	98.3±1.12	89.45±4.61	98.1±1.48
105 min	88.1±3.87	96.6±2.15	87.1±3.20	96.88±2.61	88.2±4.69	97.9±1.43	88.65±5.34	97.9±2.36
120 min	88.7±4.6	96.9±2.78	88.8±3.52	98.2±1.33	86.4±4.72	98.1±1.31	89.4±4.98	97.5±2.41

Table 3: Comparison of the duration of analgesia (in minutes) in various groups.

Study group	Duration of analgesia (in a min.)	P value (one way ANOVA)
Group I (100i.u. Calcitonin)	230.00±92.39	<0.001
Group II (placebo)	159.25±21.59	0.017
Group III (50 i.u. Calcitonin)	161.50±31.20	0.030
Group IV (control group)	142.75±20.22	Baseline

The mean duration of analgesia (in minutes) among group I (100IU calcitonin) was 230.00±92.39, 159.25±21.59 among group II (Placebo), 161.50±31.20 among group III (50IU calcitonin) and 142.75±20.22 among group IV.

Considering group IV (control group) as base line. The differences of duration of analgesia (in minutes) in group I, group II and group III with baseline value (group IV) were statistically significant (P value <0.05). Simialr results were observed in studies by Miralles FS et al and Moraby et al.^{10,11}

The observed side effects of salmon calcitonin administration are as shown in Table 4. Three (15%) cases in group I and group III; four patients in group IV; five in group II had hypotension at some point of time during the procedure which was easily managed by volume resuscitation and use of injection mephentermine 5mg intravenously. The incidence of hypotension in group II was statistically significant (p <0.05) as compared to other groups. However, there was an insignificant difference (p >0.05) in incidence among other groups.

Table 4: Comparison of adverse effect across the groups (N=80).

Adverse effect	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)
Restlessness	5 (25%)	0 (0%)	1 (5%)	0 (0%)
Hypotension	2 (10%)	5 (25%)	3 (15%)	4 (20%)
Hypoxia	0 (0%)	2 (10%)	1 (5%)	0 (0%)
PONV	6 (30%)	1 (5%)	2 (10%)	2 (10%)
Urinary retention	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Bradycardia	0 (0%)	0 (0%)	2 (10%)	2 (10%)
No untoward side effects	7 (35%)	11 (55%)	11 (55%)	12 (60%)

The incidence of hypoxia/respiratory depression was two (10%) in group II as compared to one (5%) in group III which was managed by supplementing with oxygen through venti-mask and none had this complication in group I and IV. However, there is no statistically significant difference in incidence among the groups.

Nausea and vomiting occurred in six (30%) in group I which was relieved by injection of ondansetron 0.1mg/kg intravenous as compared to one (5%) in group II, two (10%) in group III and IV. The incidence of nausea and vomiting was highly significant ($p < 0.05$) in group I as compared to other groups. However, there is the insignificant difference in incidence between group II and group III ($p > 0.05$). Restlessness/agitation occurred in five (25%) in group I as compared to one (5%) in group III, and none having this complication in group II and IV. This was highly significant ($p < 0.05$). Restlessness was relieved with an injection of midazolam 1-2mg intravenous. Urinary retention occurred in 1 (5%) in group II but none was observed in other groups. On comparing the incidence of Urinary retention between groups I, II, III, and IV showed no significant difference.

DISCUSSION

In 1979 Wang was the first to describe the intrathecal administration of morphine. Since that time, the use of intrathecal opioids has become a widely accepted technique for providing effective postoperative pain relief.¹² However, intrathecal opioids have been found associated with a multiple of adverse side effects including respiratory depression, nausea and vomiting, sedation, pruritus and urinary retention.¹³ Several attempts have been made to reduce these adverse effects by adjusting the dose of opioid or by using different additives like clonidine, neostigmine, midazolam, ketamine etc.^{14,15} However, the analgesic effect of these additives when used intrathecal is yet to be ideal.

Salmon Calcitonin, a natural hormone has been used in the treatment of pain in various clinical conditions including osteoporosis, metastasis in the spine due to cancer, phantom limbs, and sympathetic dystrophies. Specific binding sites for calcitonin have been demonstrated in mammals both in the spinal cord and in supraspinal central nervous system centers related to pain

transmission. Its presence in nervous tissue suggest that it may have range of action that exceeds its role in calcium and phosphorus metabolism.¹⁶⁻¹⁹

A nonopioid analgesic pathway has been suggested as calcitonin induced analgesic effect is not modified by opioids antagonists.²⁰ Other pathways suggested so far increases in the plasma beta-endorphin levels at the hypothalamus and/or the pituitary level, involvement of the serotonergic system.²¹⁻²³

The present study shows good analgesia and increases in the duration of the first dose of postoperative analgesia with increasing dose of salmon calcitonin from 50IU to 100IU. and same has been observed in experimental studies carried out by injecting Salmon calcitonin directly into the lateral cerebral ventriculi in rats and was suggested to be because of correspondingly increasing inhibitory and long-lasting effects on the evoked firing, with a significant dose-effect relationship.¹⁹

In our study with the use of 100IU salmon calcitonin the duration of analgesia following subarachnoid block was 230 ± 92.39 minutes which is slightly less though nearly similar to that observed by Moraby et al but, the standard deviation of 2.39min suggested that the postoperative analgesic effects were quite variable and was found to quite long lasting in some patients.¹¹ Miralles et al in their group of patients have used 100IU.¹⁰ of salmon calcitonin mixed with 5% lignocaine given intrathecally also observed that the patient treated with salmon calcitonin had significantly less pain at 6hours and even the request for analgesic was significantly less frequent.

As the incidence of hypotension between the group I and III was similar it suggests that calcitonin results in minimal cardiorespiratory depression and are independent of the dose administered. The level of sensory block, hemodynamic stability, and quality of intraoperative surgical anesthesia achieved among every four groups was similar and nonsignificant.

The adverse events reported in the earlier studies after intrathecal administration of Salmon calcitonin are nervousness, mild abdominal pain, nausea, and vomiting.^{9,10} In our study, 5 patients were observed to have restlessness in group I as compared to one in group

III group and none in other groups. There is an increase in restlessness with the use of increased dose and the incidence in this series is similar to the one observed by Miralles FS et al and Moraby et al, but the restlessness could easily be attenuated with the use of midazolam 1-2mg intravenously.^{10,11} In this study, six patients in group I had nausea and vomiting and was higher when compared with group III where only 2 patients had nausea and vomiting. The incidence of nausea and vomiting with the subarachnoid block is highly variable and has been reported to occur in about 20% of the patient. Though the incidence of nausea and vomiting is quite as high as observed by Miralles FS et al in their group of patients (6.6%) but is comparable to that observed by Rastogi et al (30%).¹⁰ The mechanism of the calcitonin leading to nausea and vomiting is not understood but as it got relieved by 5-HT3 antagonist it could be mediated through central activation of 5-HT3 receptor.²⁵

CONCLUSION

In summary, although the exact mechanism of action of intrathecal calcitonin is not properly understood, from this study we can conclude that the intrathecal salmon calcitonin can be used as an adjuvant to the local anesthetic agent to prolong the duration of analgesia in a dose-dependent proportion. Though more clinical and experimental studies are further required to understand the mechanism of action, effect and side effect associated with its intrathecal administration.

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