A Comparative Study Of Premedication For Prevention Of Vomiting Induced By Intrathecal Calcitonin: A Double Blind Study
V Rastogi, R Dutta, G Kumar

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Abstract
Background: The aim of this study was to study the complications and to compare the effects of the antiemetic premedication on incidence of nausea and vomiting induced by sub-arachnoid bupivacaine and calcitonin.

Material and Method: In a prospective, double-blind, randomized sequential allocated study, 80 ASA I and II physical status patients received 0.5% bupivacaine with 100 i.u salmon calcitonin in sub-arachnoid space and were divided into four groups of 20 each. Group I received chlorpromazine, Group II received dexamethsone, Group III received Granisetron, and Group D received no antiemetic as premedication.

Results and Conclusion: The incidence of postoperative nausea vomiting is highly variable following subarachnoid blockade with a further increase in incidence observed upon addition of additives to increase the duration of analgesia. Granisetron is a potent antiemetic among dexamethsone and chlorpromazine for prevention of postoperative nausea vomiting.

INTRODUCTION
Spinal anesthesia developed in the latter part of 18th century when Bier and Hildebrandt injected cocaine into their cerebrospinal fluids. This was a milestone in the history of anesthesia. The recent trends in the practice of spinal anaesthesia is towards addition of adjuvant like, Opioids, Ketamine, Clonidine, Midazolam, and Neostigmine etc to the local anesthetic agent to increase the efficacy and duration of analgesia longer into postoperative period.

Recently, Calcitonin a natural hormone has been demonstrated to relieve pain independent of its peripheral action on bones its analgesic effects have been shown to be comparable with sub-arachnoid fentanyl (M Moraby et al 2007) though, there are certain adverse effects e.g., nausea, vomiting, hypotension, excitement.

The incidence of postoperative nausea vomiting following neuraxial blockade is highly variable and ranges from 10% (Carpenter et al, 1978) to as high as 58% (Abouleish, E et al 1999). David L Brown has also mentioned that nausea and vomiting may be associated with neuraxial block in up to 20% patients.

This incidence is further affected by the additives used to increase the duration of analgesia. Morphine a commonly used adjuvant is associated with PONV, itching, sedation, respiratory depression and urinary retention. Kalso et al (1983) compared the quality of analgesia and incidence of adverse effects with varying doses of morphine observed that increasing the dose does not lead to an increase in the duration of analgesia but lead to an increase in incidence of postoperative nausea and vomiting(40%) in orthopedic surgery. In a similar study by Milner, A.R et al (1996) observed an incidence of (14%) which further increased (28%) upon increasing the doses of morphine. Later, Jacobson et al (1988) reported PONV rates of 60 v/s 50 v/s 100% after 0, 0.3, and 1 mg morphine respectively, used in joint replacement surgery. Weber et al (1998) conducted a large investigation involving 300 patients undergoing major orthopedic surgery of the lower extremities, comparing bupivacaine to bupivacaine with 0.2 mg morphine. observed no statistically significant difference between groups with regard to subjective feeling or consumption of antiemetics. Habib AS et al (2005) used 50 µg intrathecal morphine for analgesia after post-partum bilateral tubal ligation and
observed an incidence of 21.4%.

Fenatnyl is another most commonly used opioid though incidence of postoperative nausea vomiting after its use is not thoroughly investigated. Nimi et al (1993) observed an incidence of 30% after 24h of intrathecal fentanyl infusion. Dahl JB et al (1999) observed 60-80% of incidence of postoperative nausea and vomiting after addition of intrathecal opiates to bupivacaine. They further observed that the incidence were much higher when morphine was used as, compared to fentanyl, sufentanil and the incidence of PONV is directly proportional to the dose of the opioid administered.

There have been very few studies over Calcitonin intrathecal use (Miralles F et al, 1987) tested analgesic effects of subarachnoid administration of salmon calcitonin in acute postoperative pain and observed side effects such as nausea and vomiting and nervousness were observed in a small number of salmon calcitonin treated patients. M Moraby et al 2007 observed postoperative nausea and vomiting in 30% of patient who were provided with salmon calcitonin mixed with bupivacaine.

This study was carried out to look for the agent among Granisetron, Dexamethasone and, Chlorpromazine that can counteract nausea and vomiting associated with the intrathecal administration of Calcitonin.

**MATERIAL AND METHOD**

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 to this study were explained of the anesthetic procedure and informed consent was taken.

In this prospective, randomized sequential allocation study eighty patients of ASA grade I and II physical status undergoing surgery less than 3 hrs were enrolled. Any patient who fulfilled the following criteria was included in this study.

Patient ASA I and II, Age 18-60 yrs, Patient who was planned for elective surgery of the lower abdomen and lower extremities including, gynecological, orthopedics, urology and general surgery and as such required a subarachnoid block.

Exclusion criteria for the study were: Patient refusal, ASA III and IV, Hypovolumia, Bleeding diathesis, Sepsis, Valvular heart disease, Pregnant patient, Any disease condition predisposing to nausea and vomiting, Raised intracranial pressure, Local skin infection at spinal level L5-S1, Any other neurological disorder of the extremities or deformity of spines, Diabetics and, Hypertensive patients.

All patients were premedicated with oral alprazolam 0.5 mg on eve of surgery and 2 hrs prior to morning surgery with few sips of water. The patients were randomly allocated into four group according to the drug used:

Group I: patient receiving subarachnoid block with 0.5% heavy Bupivacaine (3.0 ml) to 1 ml of Calcitonin (100 i.u) with Chlorpromazine as antiemetic 25 mg i.v.

Group II: patient receiving subarachnoid block with 0.5% heavy Bupivacaine (3.0 ml) to 1 ml of Calcitonin (100 i.u) with Dexamethasone as antiemetic 8 mg i.v.

Group III: patient receiving subarachnoid block with 0.5% heavy Bupivacaine (3.0 ml) to 1 ml of Calcitonin (100 i.u) with Granisetron as antiemetic 1 mg i.v.

Group IV: patient receiving subarachnoid block with 0.5% heavy Bupivacaine (3.0 ml). With 1 ml of Calcitonin (100 i.u) with no antiemetic.

Patients were randomly allocated to each group. 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 by using 3.0 ml of Bupivacaine with Calcitonin 100 i.u (1 ml) and then it was put into the sub arachnoid space. Prior to putting the intrathecal Calcitonin patient was inquired about 8 hour fasting period and were being asked to void the bladder, and a subcutaneous infiltration of Calcitonin was done to look for an immune response to the protein antigen before injecting in the intrathecal space. Intravenous access using an 18-gauge cannula and a fluid of 10-12 ml/kg crystalloid was used to preload the patients.

All the patients in each of the group received their antiemetic with the establishment of i.v line before starting the procedure. Patient's baseline non-invasive arterial pressure, pulse rate saturation and a continuous ECG monitoring were instituted. In a left lateral position or sitting position, skin was cleaned and draped. After infiltrating the skin and
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interspinous ligament over the L3-4 interspace with 2% lidocaine 2 ml, the subarachnoid space was entered using a 25-gauge pencil point spinal needle. Once free flow of CSF has been recognized from the intrathecal space, anaesthetic solution was injected over 20 seconds, aspirating CSF at the beginning and end of the injection to confirm needle position.

Any episode of nausea and vomiting for the first three hours since, the instillation of drug was noted. This has been called as early vomiting. Patients were than followed in the immediate postoperative period and any nausea, vomiting episode was noted for the next 24 hours. This was called as delayed vomiting.

The observation in various groups was compared statistically using student’s test and analyzed by SPSS software of windows XP 2000.

OBSERVATION AND RESULT

The patient’s demographic data were observed for heart rate, mean blood pressure, oxygen saturation, duration of surgery, and complications including nausea and vomiting, respiratory distress, restlessness, hypotension, pruritus and sedation.

Mean Age, Sex, Height, Weight, intraoperative heart rate, blood pressure (mean), oxygen saturation, duration of surgery were comparable among all the and was non-significant.

Figure 1
Table 1

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>AGE (years) (Mean ± SD)</th>
<th>SEX(M:F) (Mean #)</th>
<th>BMI (Mean ± SD)</th>
<th>Duration of surgery (min) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>41.5±4.1</td>
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<td>26.5±4.1</td>
<td>65.2±14.3</td>
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<tr>
<td>II</td>
<td>43.6±5.3</td>
<td>128 (105:23)</td>
<td>26.3±4.2</td>
<td>65.3±15.2</td>
</tr>
<tr>
<td>III</td>
<td>47.8±6.9</td>
<td>178 (135:43)</td>
<td>26.9±4.7</td>
<td>65.5±15.8</td>
</tr>
<tr>
<td>IV</td>
<td>48.3±5.4</td>
<td>168 (135:33)</td>
<td>26.5±4.3</td>
<td>65.0±13.3</td>
</tr>
</tbody>
</table>

DISCUSSION

Postoperative nausea and vomiting continues to be a limiting factor in the early discharge, expanded nursing care and can lead to patient distress - all factors may increase total health care costs. Since the introduction of intrathecal and epidural morphine in 1979, a multitude of medication, such as synthetic opioids, alpha-2 agonists, cholinesterase inhibitors and have been introduced to augment postoperative pain relief is also associated with significant incidence of PONV. (60-80% .Dahl JB et al, 1999) Salmon Calcitonin, a natural hormone of the body which is used in the treatment of pain in various clinical conditions including osteoporosis, metastasis in spine due to cancer, phantom limbs, sympathetic dystrophies is also used in postoperative pain
relief. The probable mechanism of action is not very clear till date, but evidence suggest that its role as a new neurotransmitter (Fisher et al, 1981). Franceschini et al, 1993 and Kyviaki Mystakidou et al, 1999 have observed an increase in the plasma beta-endorphin levels acting at the hypothalamus or the pituitary through monoaminergic neurotransmitters.

In this study, populations in all the four groups were nearly comparable in their baseline age, sex, weight, height, duration of the surgical procedure, height of the blockade, VAS at the end and 3 hours after the procedure

Fujii Y et al (1998) studied the minimum effective dose of granisetron in non emergent caesarean section carried out under regional anaesthesia observed that the incidence of nausea and vomiting was 64% in placebo, 52%, 14% and 12% in 20µg/kg, 40µg/kg, 80µg/kg. Later in another study, he observed that prophylactic granisetron reduce the dose requirement of antiemetic by 85% as compared to 45% in the placebo. The antiemetic efficacy of the granisetron observed in above studies is quite comparable to our study where only 15% of patient developed intraoperative nausea and vomiting and also statistically significant (p<0.05) antiemetic effect compared to control group (45% incidence), chlorpromazine group (35%) and dexamethasone group (40%). In the first 24 hrs, study patients with no PONV were 90% in granisetron group, 85% in chlorpromazine group, 80% in dexamethasone group, and 70% in control group showing its prolonged antiemetic effect.

Similarly, chlorpromazine when used alone has shown to reduce the incidence of postoperative nausea vomiting to 20-30% (60% with placebo) by Liu K et al (1998), Wang JJ et al (1999). However, later on Szarvas S et al (2003) observed that 63% of their orthopedic patients who received intrathecal morphine and dexamethasone as an antiemetic developed postoperative nausea and vomiting within first 24 hours. On comparing with chlorpromazine group, its antiemetic efficacy is nearly similar. However, on comparing with the granisetron, antiemetic efficacy of dexamethasone is far more superior to that of chlorpromazine group. This is quite comparable to that seen previously also in various studies like Fujii Y et al (1999).

In our study, only 2.2% developed intraoperative restlessness. Earlier, Miralles FS et al (1987) also observed restlessness in 29.7% after giving intrathecal calcitonin. Later, Moraby et al (2007) also observed intraoperative restlessness in 20% patients that is quite higher than that observed in the present study. The cause of this intraoperative restlessness is still not properly understood. The intraoperative cardiovascular stability in all the four groups was assessed by heart rate and blood pressure. No significant difference (p<0.05) in heart rate, blood pressure was observed in any of the four groups for the duration of the procedure and the result were comparable to that seen by F S Miralles et al (1987), M Moraby et al (2007).

CONCLUSION

The development of 5-HT3 antagonists drugs, of which granisetron is the most widely used, offers a novel and possibly more effective approach to control peri-operative nausea and vomiting as compared to chlorpromazine and dexamethasone.

References
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