"Protective Premedication": A Comparative Study of Acetaminophen, Gabapentin and Combination of Acetaminophen with Gabapentin for Post-Operative Analgesia

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ABSTRACT

Background: We carried out a study to evaluate the effects of protective premedication with Acetaminophen, Gabapentin and combination of Acetaminophen with Gabapentin on post-operative analgesia in patients undergoing open cholecystectomy under general anesthesia.

Patients & Methods: The study was conducted in a double-blind randomized and controlled manner in 120 consenting patients of either sex belonging to ASA physical status grade I and II, between the age groups of 20 to 50 years, weighing between 40 to 65 kg and undergoing elective surgery (open cholecystectomy) under general anesthesia. The patients were divided into 4 groups: 1: placebo, 2: Acetaminophen 1000 mg, 3: 1200 mg Gabapentin, 4: Acetaminophen 1000 mg plus 1200 mg Gabapentin. The drugs were given two hours before induction. Time, number and total amount of rescue analgesic (tramadol) and VAS score at rest and on movement. Side effects like any episode of nausea/vomiting and level of sedation were noted.

Results: Premedication with antihyperalgesic and analgesic agents helps to decrease postoperative pain scores. Gabapentin premedication is effective for providing better postoperative pain relief with lower and delayed requirements of rescue analgesics, but causes more episodes of nausea and vomiting and higher levels of sedation.

KEYWORDS: Premedication, Gabapentin, Acetaminophen

It is the indictment of modern medicine that an apparently simple problem such as the reliable relief of post-operative pain remains unsolved, despite advances in the knowledge of pathophysiology of pain, pharmacology of analgesics and the development of more effective techniques for control of post-operative pain.

The concept of pre-emptive analgesia, which is an analgesic treatment before giving a surgical stimulus, was introduced to protect the central nervous system from deleterious effects of noxious stimulus and the patient from the resulting hyperalgesia and allodynia.

Gabapentin introduced in late 1980’s was initially approved only for use of partial seizures but was soon found to be promising in treating neuropathic pain1-3. Recently, several reports have also indicated that oral Gabapentin may have a place in treatment of post-operative pain4-16. In these studies patients received Gabapentin orally in a dose range of 300 to 1200 mg as premedication one to two and half hours before surgery.

Acetaminophen (Paracetamol) is being used safely for a long time as an analgesic in all age groups17,18. Review of literature reveals that no definitive study has been carried out, to evaluate the post-operative analgesic effect of combination of Acetaminophen with Gabapentin given pre-operatively.

For the reasons as stated above, it was proposed to carry out a study in a double-blind, randomized and controlled manner to evaluate the effects of protective premedication with Acetaminophen, Gabapentin and combination of Acetaminophen with Gabapentin on postoperative analgesia in patients undergoing open cholecystectomy under general anesthesia.

PATIENTS AND METHODS

The study was conducted in a double-blind randomized and controlled manner in 120 well informed consenting patients of either sex belonging to ASA physical status grade I and II, between the age groups of 20 to 50 years, weighing between 40 to 65 kg and undergoing elective surgery (open cholecystectomy) under general anesthesia.

Patients on chronic analgesic therapy, MAO inhibitor therapy, corticosteroids or taking any other drugs acting on central nervous system, patients suffering from nausea/vomiting, pregnant or lactating patients and patients with known allergy to Gabapentin were excluded from study.

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The 11 point, 100 mm VAS was used and shown to all the patients on pre-operative visit, its two end points: 0 or 100 corresponding to “No Pain” or “Worst Imaginable Pain” respectively.

The study was conducted in a double-blinded manner. 120 envelopes were prepared, coded as Group-I, Group-II, Group-III and Group-IV (30 envelopes for each group), were sealed and opened for each patient to indicate the group of assignment. Identical looking control and / or treatment capsules for each group were packed in group specific bottles and coded as bottle I, Bottle II, Bottle III and Bottle IV for Group I, II, III and IV respectively. The placebo capsules were filled with thin sugar. Envelopes, bottles with capsules and coding were prepared by an anesthesiologist who was not participating in the study, evaluation of patients or data or in reporting of the findings. The investigator observing the results or any other medical or nursing staffs were not aware of the treatment administered to any patient.

All the patients were blindly randomized to one of the following four groups depending on the drug combinations. (1) Placebo/control group: Patients received 5 placebo capsules.

(2) Acetaminophen group: Patients received 1000 mg of Acetaminophen (Crocin, 500 mg tablet, Glaxo-Smithkline Pharmaceuticals Ind. Ltd.) crushed and packed in 5 capsule.

(3) Gabapentin group: Patients received 1200 mg of Gabapentin (Gabapin, 400mg Capsule; Intas Pharmaceuticals Ltd, India) packed in 5 capsules.

(4) Acetaminophen plus gabapentin group: Patients received 1000 mg of crushed Acetaminophen tablets and 1200 mg of Gabapentin, packed in 5 capsule shells.

The patient was given 0.25mg alprazolam tablet on the night before surgery. Patient were kept nil per orally for eight hours prior to surgery. Intravenous line with Lactated Ringer’s Solution was started using 18G intravenous canula. Mean Blood Pressure (B.P.), heart rate (HR), oxyhaemoglobin saturation (SPO₂), respiratory rate (RR), VAS score at rest and on movement and level of sedation were recorded before administration of the drug and time of administration was noted. Two hours before induction of anaesthesia patient was given five identical looking capsules with 20ml of water, according to the group in chosen envelope.

The patient was shifted to operation table and was connected to monitor for continuous monitoring of mean blood pressure (every 3 minutes), heart rate (HR), ECG (Lead-II), end tidal carbon dioxide (ETCO₂) and oxyhaemoglobin saturation (SPO₂). The patient was given 10mg of metoclopramide (Perinorm, injection, IPCA Laboratories Ltd.) intravenously for prevention of gastro-esophageal reflux and vomiting. Blood pressure (mean), heart rate, oxyhaemoglobin saturation, respiratory rate, VAS score at rest and on movement and level of sedation were recorded before induction of anesthesia.

Surgery was conducted in similar way in all patients using thiopentone (5 mg kg⁻¹ i/v), atracurium (0.5 mg kg⁻¹ i/v), patazocine (0.5mg kg⁻¹ i/v) and maintained with isoflurane (0.5-1%) and nitrous oxide (66%) in oxygen. Patients were reversed with 0.05mg kg⁻¹ Neostigmine and 0.02mg kg⁻¹ Atropine.

Heart rate (HR), B.P., SPO₂, respiratory rate (RR), VAS score at rest and on movement, any episode of nausea/vomiting and level of sedation were noted on arrival to the PACU and this was recorded as the baseline score (0 hours). These were also noted hourly for 4 hours and subsequently at 6, 8, 12, 16, 20 and 24 hours.

Tramadol was used as rescue analgesic based on patient’s demand and the time and frequency and total consumption of rescue analgesic was noted. The VAS scale at time of rescue analgesic was also noted at rest as well as on movement. Injection Tramadol 1mg kg⁻¹ was given over 2-3 minutes intravenously and after a further 30 minutes VAS was observed. Further increment of 20 mg was given if VAS = 40mm and the total dose (maximum 400 mg/24 hours) were recorded.

The occurrence of any untoward side effects, such as dizziness, nausea, vomiting, somnolence, diarrhea, sedation, restlessness, etc. was also recorded.

Nausea and vomiting was assessed using a 5 point scale. Two or more emetic episodes were treated with Intravenous metoclopramide 0.2mg kg⁻¹.

Sedation was scored using Ramsay sedation score. RESULTS

Demographic data (patient characteristics and duration of surgery) was comparable in all the groups (Table 1).

The average time of first rescue analgesic consumption for group 1, 2, 3 and 4 was 66.17 ± 55.28, 90.17 ± 51.58, 332.00 ± 149.30 and 431.33 ± 171.94 minutes respectively. When all the groups were compared together, the difference was highly significant (p-value<0.001). The average number of rescue analgesics given to the patients in group 1, 2, 3 and 4 was 3.60 ± 0.49, 3.30 ± 0.53, 1.93 ± 0.57 and 1.80 ± 0.54 respectively (significant difference when compared together). The average total rescue analgesic consumption for group 1, 2, 3 and 4 was 203.83 ± 41.55, 190.50 ± 37.62, 106.33 ± 32.07 and 99.83 ± 29.11 mg respectively (significant, when compared together). Intergroup comparisons are given in Table 2.
Visual Analogue Scale at rest (VAS-R) had significant difference when all the groups were compared together (p-value<0.01). On comparing group 1 (control) with group 2 (acetaminophen) significant difference was seen at 0, 6, 16 and 20 hours post-operatively. Similarly, highly significant difference was seen between group 1 and group 3 (Gabapentin group) at all time intervals (P=<0.01) except at 4 and 6 hours post-operatively (P>0.05). The post-operative comparison of difference in VAS-R between group 1 and group 4 (combination group) was also significant at 4 hours (P<0.05) and highly significant at all other time intervals (P<0.01). On the other hand, no significant difference in VAS-R was seen between group 3 and group 4.

The intra group comparison of pain at rest in group 1 was significant at the time of drug administration and before induction when compared with the 0 hour base line pain score. In group 2, the intra group comparison of VAS at rest was insignificant at all time intervals. In group 3, the difference in pain was significant at 8 and 12 hours and highly significant at 16 hour. Similarly, pain score was significant at 8 and 16 hours (P<0.05) on intra group comparison with 0 hour base line score in group 4 while it was insignificant at all other time intervals.

Visual analogue scale on movement (VAS-M) when compared in all the groups together had significant difference. On comparing group 1 with group 2, group 3 and group 4 the difference in pain on movement after surgery was highly significant at all times (P<0.001). The difference in VAS-M was not significant at 6 hours but was highly significant at all other time intervals on comparison between group 2 and group 3 (P<0.01). On comparing group 2 with group 4, it was significant at 6 hours (P<0.05) and highly significant at all other time intervals (P<0.01). On the other hand, no significant difference in VAS on movement was seen between group 3 and group 4.

The intra group comparison of pain at movement in group 1 was very highly significant at the time of drug administration and before induction when compared with the 0 hour base line pain score (P<0.01). Similarly, in group 2, pain scores at the time of drug administration, before induction and at 1 hour were highly significant (P<0.01) and significant (P<0.05) at 2 and 24 hours post-operatively. Pain at the time of drug administration and before induction had significant difference when all the groups were compared together (p-value<0.01). On comparing group 1 (control) with group 2 (acetaminophen) significant difference was seen at 0, 6, 16 and 20 hours post-operatively. Similarly, highly significant difference was seen between group 1 and group 3 (Gabapentin group) at all time intervals (P=<0.01) except at 4 and 6 hours post-operatively (P>0.05). The post-operative comparison of difference in VAS-R between group 1 and group 4 (combination group) was also significant at 4 hours (P<0.05) and highly significant at all other time intervals (P<0.01) except at 6 hours where the difference was insignificant (P>0.05).

On comparing group 2 with group 3, post-operative pain at rest was very highly significant at 0, 1, 2 and 24 hours (P<0.001). Similarly, comparison of group 2 with group 4 had significant difference in post-operative pain at rest at 3 hours while it was highly significant at 0, 1, 2 and 24 hours (P<0.001). On the other hand, group 3 and group 4 had no significant difference in post-operative pain at rest.

### Table 1
**Demographic Data**

| Groups | No. of Pt. | Age Mean S.D. | Weight Mean S.D. | Sex MA S.D. | FA S.D. | Height Mean S.D. | Duration of Surgery Mean S.D. |
|--------|------------|---------------|------------------|------------|---------|------------------|-----------------------------|
| 1      | 30         | 39.60 7.69    | 56.30 6.35       | 23 4.77    | 4.77    | 157.87 7.69      | 50.67                       |
| 2      | 30         | 39.20 8.07    | 57.33 5.53       | 22 5.93    | 5.93    | 158.17 8.07      | 51.33                       |
| 3      | 30         | 39.97 6.20    | 55.90 5.13       | 23 4.55    | 4.55    | 157.20 6.20      | 50.00                       |
| 4      | 30         | 40.20 8.01    | 55.90 5.88       | 23 4.73    | 4.73    | 156.93 8.01      | 50.83                       |
| P-Value| >0.05      | 0.959 0.742   | 0.250 0.758      | 0.893      | 0.893   |                   |                             |

### Table 2
**Statistical comparison of rescue analgesics in different groups**

| Groups | Time of First Rescue Analgesic 'P' value | Number of Rescue Analgesics 'P' value | Total amount of Rescue Analgesics 'P' value |
|--------|-----------------------------------------|--------------------------------------|--------------------------------------------|
| 1 Vs 4 | <0.001                                  | <0.001                               | <0.001                                     |
| 1 Vs 3 | <0.001                                  | <0.001                               | <0.001                                     |
| 1 Vs 2 | 0.866                                   | 0.135                                | 0.466                                      |
| 2 Vs 4 | <0.001                                  | <0.001                               | <0.001                                     |
| 2 Vs 3 | <0.001                                  | <0.001                               | <0.001                                     |
| 3 Vs 4 | 0.009                                   | 0.781                                | 0.893                                      |

Visual Analogue Scale at rest (VAS-R) had significant difference when all the groups were compared together (p-value<0.01). On comparing group 1 (control) with group 2 (acetaminophen) significant difference was seen at 0, 6, 16 and 20 hours post-operatively. Similarly, highly significant difference was seen between group 1 and group 3 (Gabapentin group) at all time intervals (P=<0.01) except at 4 and 6 hours post-operatively (P>0.05). The post-operative comparison of difference in VAS-R between group 1 and group 4 (combination group) was also significant at 4 hours (P<0.05) and highly significant at all other time intervals (P<0.01) except at 6 hours where the difference was insignificant (P>0.05).

On comparing group 2 with group 3, post-operative pain at rest was very highly significant at 0, 1, 2 and 24 hours (P<0.001). Similarly, comparison of group 2 with group 4 had significant difference in post-operative pain at rest at 3 hours while it was highly significant at 0, 1, 2 and 24 hours (P<0.001). On the other hand, group 3 and group 4 had no significant difference in post-operative pain at rest.

### Table 3
**Post-operative nausea/vomiting**

| Group | Total No. of Patients | No. of Patients | Grades | % | P Value |
|-------|-----------------------|-----------------|--------|---|---------|
| Group 1 | 14                    | 2               | Grade 1 | 14.29 | 0.910 |
|       | (46.67%)              | Grade 2        | 7.14   |    |         |
|       | P – 0.796             | Grade 3        | 42.86  |    |         |
|       |                       | Grade 4        | 35.71  |    |         |
| Group 2 | 14                    | 1               | Grade 1 | 7.14 | 0.175 |
|       | (46.67%)              | Grade 2        | 21.43  |    |         |
|       | P – 0.796             | Grade 3        | 42.86  |    |         |
|       |                       | Grade 4        | 28.76  |    |         |
| Group 3 | 25                    | 0               | Grade 1 | 0.00  | <0.001 |
|       | (83.33%)              | Grade 2        | 4.00   |    |         |
|       | P - 0.007             | Grade 3        | 12.00  |    |         |
|       |                       | Grade 4        | 84.00  |    |         |
| Group 4 | 25                    | 1               | Grade 1 | 4.00 | <0.001 |
|       | (83.33%)              | Grade 2        | 0.00   |    |         |
|       | P - 0.007             | Grade 3        | 20.00  |    |         |
|       |                       | Grade 4        | 76.00  |    |         |
| P Value |                      |                 |        | <0.001 |         |
before induction was significant (P<0.05) and extremely significant (P<0.01) at all other time intervals both in group 3 and group 4.

The difference of incidence of PONV (Table 3) in group 3 and group 4 was very highly significant in comparison to control group and acetaminophen group. The intra group comparison of PONV both in group 3 and group 4 was very highly significant (P<0.001).

While comparing sedation levels (Table 4), the intra group difference in all the groups was very highly significant (P<0.001). On comparing together with respect to patients asleep (Ramsay 4 or more), the difference in the number of patients was highly significant (P<0.01).

### Table 4

| Post-Operative Sedation | Total No. of Patients | No. of Levels | % | P Value |
|-------------------------|-----------------------|---------------|---|---------|
| Group 1                 | 29                    | 0 Level 1     | 0.00 | <0.001 |
|                         |                       | 2 Level 2     | 6.90 |
|                         |                       | 8 Level 3     | 27.59 |
|                         |                       | 17 Level 4    | 58.62 |
|                         |                       | 2 Level 5     | 6.90 |
|                         |                       | 0 Level 6     | 0.00 |
| Group 2                 | 30                    | 0 Level 1     | 0.00 | <0.001 |
|                         |                       | 0 Level 2     | 0.00 |
|                         |                       | 8 Level 3     | 26.67 |
|                         |                       | 18 Level 4    | 60.00 |
|                         |                       | 4 Level 5     | 13.33 |
|                         |                       | 0 Level 6     | 0.00 |
| Group 3                 | 30                    | 0 Level 1     | 0.00 | <0.001 |
|                         |                       | 0 Level 2     | 0.00 |
|                         |                       | 0 Level 3     | 0.00 |
|                         |                       | 4 Level 4     | 13.33 |
|                         |                       | 22 Level 5    | 73.33 |
|                         |                       | 4 Level 6     | 13.33 |
| Group 4                 | 30                    | 0 Level 1     | 0.00 | <0.001 |
|                         |                       | 0 Level 2     | 0.00 |
|                         |                       | 0 Level 3     | 0.00 |
|                         |                       | 5 Level 4     | 16.67 |
|                         |                       | 20 Level 5    | 66.67 |
|                         |                       | 5 Level 6     | 16.67 |

### DISCUSSION

Post-operative pain is one of the most feared and is probably the most prevalent of all pain conditions, yet in many cases it continues to be inadequately controlled. Various drugs through different routes have been tried to produce adequate analgesia in patients after surgery. Gabapentin is a new drug with minimal side-effects which has been used for post-operative analgesia.

Demographic variables were comparable among all the four Groups. The duration of surgery and anaesthesia were also comparable among all the four Groups (P>0.05). Fassoulaki and others\(^4\) did not observe any difference in time of first rescue analgesic consumption after pre-operative administration of 1200mg of oral Gabapentin but on the contrary Turan and associates\(^8\) found a highly significant difference between the Gabapentin and Placebo Groups. In the present study, we also observed a very highly significant difference in the time of first rescue analgesic consumption in patients who consumed Gabapentin (Group 3) and combination of Gabapentin with Acetaminophen (Group 4) in comparison to patients who consumed Placebo / Acetaminophen. There was no statistical difference in the time of first rescue analgesic consumption in patients who consumed Acetaminophen or Placebo. But when Acetaminophen was combined with Gabapentin (Group 4), the time of first rescue analgesic consumption was higher in comparison to the patients who consumed Gabapentin alone (Group 3) which indicates that Gabapentin might have potentiated the analgesic effect of Acetaminophen. Similar effect was seen in few studies where the effect of Rofecoxib\(^{16}\) and Morphine\(^3\) was enhanced by Gabapentin.

The difference in the number of rescue analgesic consumption was very significantly reduced in patients who consumed Gabapentin (Group 3) and the combination of Gabapentin with Acetaminophen (Group 4) in comparison to patients who did not consume Gabapentin. Similar results were observed in patients of ear-nose-throat surgery in a study conducted by Turan and associates\(^8\).

In the present study Gabapentin and Acetaminophen combination (Group 4) reduced the total analgesic requirement (Tramadol) by 51% in comparison to the control Group (P<0.001) and 48% in comparison to Acetaminophen Group (P<0.001). Similarly Gabapentin alone (Group 3) also reduced the Tramadol requirement by 48% on comparison with the control Group (P<0.001) and 44% in comparison to Acetaminophen Group (P<0.001). The difference in total rescue analgesic consumption noticed by addition of Acetaminophen to Gabapentin on comparison to Gabapentin alone was statistically found to be insignificant during first 24 hours post-operatively which could be because of short half life of acetaminophen of just 2-3 hours and a weak anti-inflammatory action.

Similar reduction in post-operative total rescue analgesic consumption by 32% to 62% was noticed in various research works on post-operative analgesia. Fassoulaki and associates\(^4\) on the other hand Fassoulaki and associates\(^4\) found no reduction in analgesic requirement
during first 24 hours of breast surgery for cancer but it was decreased from second to tenth day.

In the present study, patients who consumed Gabapentin alone (Group 3) had lower VAS scores at rest (VAS-R) and on movement (VAS-M) at all time intervals in comparison to the Placebo Group (Group 1). Similarly patients who consumed Gabapentin along with Acetaminophen (Group 4) had lower VAS scores at rest and on movement at all time intervals in comparison to the Placebo Group. Patients who consumed Gabapentin alone had lower VAS scores at all time intervals in comparison to the patients who consumed Acetaminophen alone (Group 2) but the difference in VAS-R was statistically significant only at 0, 1, 2 and 24 hours post-operatively while VAS-M was statistically significant at all time intervals except at 6 hours.

Similarly patients who consumed Gabapentin along with Acetaminophen had lower VAS scores at all time intervals in comparison to the patients who consumed Acetaminophen alone but the difference was statistically significant only at 0, 1, 2, 3 and 24 hours post-operatively. Patients who had Gabapentin along with Acetaminophen had lower VAS score at all time gaps except at 6, 8 and 12 hours for VAS-R and at 8 hours for VAS-M in comparison to the patients who consumed Gabapentin alone but this difference was statistically insignificant.

In discectomy/spinal fusion surgery, Turan and others noticed a reduction in pain scores during 1, 2 and 4 hours in patients of Gabapentin (1200mg one hour prior to surgery) Group. But Pandey and co-workers found a reduction in pain scores up to 24 hours post-operatively with a smaller dose of 300 mg of Gabapentin given two hours before lumbar discectomy.

On the contrary, Radhakrishnan and others found no reduction in pain scores for eight hours post-operatively in patients who underwent lumbar laminecctomy and discectomy after two divided doses of Gabapentin of 800mg in comparison to Placebo. The results of all the above mentioned studies in a similar pain model are contradictory.

Patients who consumed Gabapentin (Group 3 and Group 4) did not have much difference in pain intensity at rest in comparison to pain on movement at any time during 20 hours post-operatively while it was significant at 24 hours. Statistically insignificant difference in pain at rest and on movement (less pain on movement) signifies the potent effect of Gabapentin on post-operative pain.

Patients who consumed Acetaminophen had significant or highly significant difference in pain scores at rest on comparison with pain scores on movement except at 0 hours. The inability of acetaminophen to decrease post-operative pain on movement reveals its weak anti-inflammatory action. Similar effect on post-operative pain on activity was noticed in various research works. But Fassoulaki and others found reduction in pain on movement only from second to fifth day following breast surgery for cancer.

In the present study, the main side-effect that was noticed as a result of consumption of Gabapentin was post-operative nausea / vomiting. Incidence of PONV in patients who consumed Gabapentin was 36.66% higher than the patients who were given Acetaminophen / placebo (P<0.001). Use of tramadol as rescue analgesic in the present study might have increased the incidence of PONV. Similar statistically significant increase in the incidence of PONV was also noticed in few studies of post-operative analgesia.

Sedation was discovered to be another major drawback due to consumption of Gabapentin. A significantly high number of patients (100%) in Group 3 and Group 4 (patients who consumed Gabapentin) had sedation of level 4, 5 or 6 in comparison to 65.52% patients in Group 1 and 73.33% patients in Group 2 (patients who did not consume Gabapentin).

Similar increase in level of sedation as a result of administration of Gabapentin was noticed in some research works of post-operative analgesia while no significant difference was noticed in few other studies.

The above mentioned results of our study demonstrated that it may be possible to protect the patient and the patient's nociceptive system, from the negative effects of noxious stimuli by protective premedication with combination of various antihyperalgesic and analgesic drugs and Gabapentin is a useful agent for the same.

REFERENCES
1. Parsons B, Tive L, Huang S. Gabapentin: A pooled analysis of adverse events from three clinical trials in patients with postherpetic neuralgia. Am J Geriatr Pharmacother. 2004; 2: 157-62.
2. Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with Gabapentin. Arch Phys Med Rehabil 1997; 78: 98-105.
3. Caraceni A, Zecca E, Bonezzi C, Arcuri E, Yaya Tur R, Maltoni M. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol. 2004; 22: 2909-17.
4. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of Gabapentin and Mexiletine after breast surgery for cancer. Anesth Analg 2002; 95: 985-91.

5. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single dose Gabapentin versus placebo on post-operative pain and Morphine consumption after mastectomy. Anesthesiology 2002; 97: 560-4.

6. Dierking G, Duedahl TH, Rasmussen ML, Fomsgaard JS, Moonachie S, Romsing J, et al. Effects of Gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: a randomized, double blind trial. Acta Anaesthesiol Scand 2004; 48: 322-7.

7. Turan A, Karamanlioglu B, Memis D, Hamamcioglu MK, Tukenmez B, Pamukcu Z and others. Analgesic affect of Gabapentin after spinal surgery. Anesthesiology 2004; 100: 935-8.

8. Turan A, Memis D, Karamanlioglu B, Yagiz R, Pamukcu R, Yavuz E. The analgesic effect of Gabapentin in monitored anaesthesia care for Ear-Nose-Throat surgery. Anesth Analg 2004; 99: 375-8.

9. Rorarius MGF, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R and others. Gabapentin for prevention of post-operative pain after vaginal hysterectomy. Pain 2004; 110: 175-81.

10. Turan A, Karamanlioglu B, Memis D, Usar P, Pamukcu Z, Ture M. The analgesic effect of Gabapentin after total abdominal hysterectomy. Anesth Analg 2004; 98: 1370-3.

11. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, et al. Preemptive Gabapentin decreases post-operative pain after lumbar discectomy. Can J Anaesth 2004; 51: 986-989.

12. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of Gabapentin significantly decreases post-operative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004; 51: 358-63.

13. Gilron I, Orr E, Tu D, Neill P, Zamora J, Bell A. A placebo controlled randomized clinical trial of perioperative administration of Gabapentin, Rofecoxib and their combination for spontaneous and movement evoked pain after abdominal hysterectomy. Pain 2005; 113: 191-200.

14. Radhakrishan M, Bithal PK, Chatruvedi A. Effect of preemptive Gabapentin on post-operative pain relief and Morphine consumption following lumbar laminectomy and discectomy. J Neurosurg Anesthesiol. 2005; 17: 125-28.

15. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB and others. Evaluation of the optimal preemptive dose of Gabapentin for post-operative pain relief after diskectomy. J Neurosurg Anesthesiol 2005; 17: 65-68.

16. Al-Mujadi H, A-Refai AR, Katzarov MG, Dehrab NA, Batra YK, Al-Qattan AR. Preemptive reduces postoperative pain and opioid demand following thyroid surgery. Can J Anaesth 2006; 53:268-73.

17. Hahn TW, Mogensen T, Lund C, Schouenborg L, Rasmussen M. High-dose rectal and oral acetaminophen in post-operative patients – serum and saliva concentrations. Acta Anaesthesiol Scand 2000; 44: 302-306.

18. Lipton R, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine. Arch intern med. 2000; 160: 3486-92.

19. Peerman MH. Single dose intravenous ondansetron in the prevention of post-operative nausea and vomiting. Anaesthesia 1994; 49: 16-23.

20. Ramsay MA, Savege TM, Simpson BR. Controlled sedation with alfaxalone–alphadolone. BMJ 1974; 2: 656-59.