A Randomized Double Blind Placebo Controlled Study Of Prophylactic Gabapentin For Prevention Of Postoperative Pain And Morphine Consumption In Patients Undergoing Mastectomy.

A Butt, K Mohammad, M Ommid, M Ahmad, N Jehan, S Qazi

Citation

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Abstract

Background:

Gabapentin, an antiepileptic has over the years been used as an analgesic. It is known to have opioid sparing properties thereby reducing the use of narcotic analgesic in the perioperative period.

Method:

: 50 patients each of ASA I–II were randomly allocated to two study groups- one group received gabapentin (1200mg) and other group received placebo 1 hour prior to surgery. Both groups received morphine (0.1mg/kg) as intraoperative analgesic at induction of anaesthesia. After the completion of mastectomy postoperative analgesia was assessed with visual analogue scale (VAS) method (0cm- no pain and 10cm- worst possible pain). Rescue analgesic was administered to patients whose VAS was above 3 (morphine 0.1mg/kg). Apart from VAS haemodynamic parameters and oxygen saturation were regularly recorded half hourly for first two hours, then hourly for next 4 hours and then 2 hourly till the patient requested for analgesia postoperatively.

Result:

: There was a statistically significant difference (p < 0.05) among the two groups as regards the intraoperative and postoperative heart rates. Systolic blood pressure showed significant variation (p < 0.05) among the two groups.

Conclusion:

: Prophylactic use of oral gabapentin prior to surgery reduced the incidence of pain and significant degree of analgesia was achieved in such patients as compared to placebo group. Prophylactic use of oral gabapentin before mastectomy reduced the overall consumption of morphine as well as incidence of postoperative pain.

INTRODUCTION

Proper postoperative pain relief is a major concern worldwide. Pain is tagged as one of the most distressing symptoms of most maladies and adequate air control is imperative in the care of surgical patients (1,2). Despite improved analgesics and sophisticated drug delivery systems, surveys indicate that 86% of patients experience moderate to severe pain after surgery (3).

Discovery of opioid receptors in the brain and spinal cord has led to the introduction of new methods for the management of pain (4,5). The concept of pre-emptive analgesia suggests that the best postoperative pain management begins preoperatively (6). Gabapentin can reduce the neuroendocrine stress response to surgery and
pain (6).

Gabapentin, an anticonvulsant introduced in 1993 has been recently used for postoperative pain (7). The therapeutic action is thought to involve voltage gated N type calcium channel (8) and has little or no abuse potential (9). Gabapentin has been shown to produce opioid sparing effects when administered to postoperative surgical patients (10).

This randomized prospective controlled study was undertaken to find and compare the analgesic efficacy of prophylactic gabapentin on postoperative pain and morphine consumption in females undergoing mastectomy.

MATERIALS AND METHODS

This prospective double blind randomized controlled study was conducted in the department of anaesthesiology and critical care at Sher-I-Kashmir Institute of Medical Sciences, Srinagar from 2008 to 2010. A proper approval from the institutional ethics committee was obtained and informed consent was taken from the patients included in the study. 100 patients of American Society of Anaesthesiologists (ASA) I & II in the age group 20-60 years, scheduled for elective mastectomy that consented were enrolled in the study. Exclusion criteria include age below 20 or above 60 years of age, morbid obesity, heart block and other conduction abnormalities, significant lung pathology, liver disease, pregnancy, history of neurological diseases and bleeding diathesis.

The patients were randomly allocated to two groups of 50 patients each. Patients allocated to the Gabapentin group received 1200mg of gabapentin orally one hour before surgery, while those in the placebo group received a placebo (capsule similar to gabapentin). All patients enrolled were reliable, cooperative and mentally capable of adhering to the protocol and provided the relevant study information for whole study period. At the preoperative visit, patients were instructed about the evaluation of pain using Visual Analogue Scale (VAS) of 0-10 cm (0= no pain and 10= worst possible pain). On the evening before surgery, all the patients were clinically evaluated, investigated and assured. The patients were advised to fast overnight.

Before arrival to the operating room all patients were administered 1200mg of gabapentin or placebo on hour before the study in a double blind fashion. The basic outcome was measurement of pain and morphine consumption from 0-12 hours postoperatively.

General anaesthesia was administered using propofol or sodium thiopentone (STP) after turning the patient to supine position and establishing an intravenous line under aseptic conditions. Analgesia during surgery was provided using 0.1mg/kg of morphine only. No analgesic was administered intraoperatively. Muscle relaxant Atracurium Besylate was used. Anaesthesia was maintained with oxygen (33%) in nitrous oxide (66%) and Halothane (<1%). Heart rate, blood pressure and SpO2 were recorded every 5 minutes until the end of surgery and intravenous fluids administered on basis of preoperative deficit, maintenance requirement and intraoperative loss.

If the patient experienced pain in the postoperative period and a request for analgesia was made with VAS more than 3, morphine 0.1mg/kg was given as rescue analgesia. Patients were monitored half hourly for first 2 hours, hourly for next 4 hours and then 2 hourly till patient requested for analgesia postoperatively. Monitoring included heart rate, blood pressure and pulse oximetry. Pain was assessed using VAS. Side effects like nausea, vomiting, dizziness, sweating and headache were recorded. Rescue analgesia needed was also noted.

After completion of the study, the data was analysed statistically. Data was presented as Mean and Standard Deviation. Student t test was used to compare the demographic data and for the incidence of postoperative pain. The test of proportion “Z test” was used to test the significance of severity of postoperative pain between the groups. P value < 0.005 was considered statistically significant. All analysis were performed with intention to treat bias.

Table 1/ Fig 1 show the comparison of intraoperative heart rate at regular intervals in comparison with the baseline. The baseline values were 97.2 ± 1.8 in the gabapentin group and 94.6 ± 1.2 in the control group. The values found at 15 minutes intraoperatively were found to have a statistically insignificant difference. Values at all other intervals after 15 min showed a statistically significant difference in comparison to baseline thereafter (p <0.05)
A Randomized Double Blind Placebo Controlled Study Of Prophylactic Gabapentin For Prevention Of Postoperative Pain And Morphine Consumption In Patients Undergoing Mastectomy.

Figure 1
Table 1: Intra operative heart rate (beats/min) of the Studied Subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.D</th>
<th>Mean</th>
<th>S.D</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>97.2</td>
<td>11.8</td>
<td>96.6</td>
<td>12.0</td>
<td>0.278 (NS)</td>
</tr>
<tr>
<td>15 min</td>
<td>98.7</td>
<td>12.3</td>
<td>95.5</td>
<td>11.4</td>
<td>0.185 (NS)</td>
</tr>
<tr>
<td>30 min</td>
<td>87.6</td>
<td>7.4</td>
<td>95.5</td>
<td>11.0</td>
<td>0.000 (Sig.)</td>
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<tr>
<td>45 min</td>
<td>82.6</td>
<td>8.8</td>
<td>96.9</td>
<td>10.3</td>
<td>0.000 (Sig.)</td>
</tr>
<tr>
<td>60 min</td>
<td>89.0</td>
<td>8.6</td>
<td>96.9</td>
<td>9.9</td>
<td>0.000 (Sig.)</td>
</tr>
<tr>
<td>75 min</td>
<td>77.6</td>
<td>7.5</td>
<td>96.9</td>
<td>10.5</td>
<td>0.000 (Sig.)</td>
</tr>
<tr>
<td>90 min</td>
<td>76.3</td>
<td>7.9</td>
<td>99.3</td>
<td>9.8</td>
<td>0.000 (Sig.)</td>
</tr>
<tr>
<td>105 min</td>
<td>77.2</td>
<td>7.1</td>
<td>100.1</td>
<td>10.6</td>
<td>0.000 (Sig.)</td>
</tr>
</tbody>
</table>

Figure 2
Fig: 1 Intraoperative heart rate (beats/min) of the studied subjects

Table 2 showing the comparison of postoperative heart rates at regular intervals in comparison with baseline with baseline values being 81.3± 9.8 in gabapentin and 85.6 ± 10.6 in the control group. All values after 60 min postoperatively showed a difference when compared with the baseline statistically.

Figure 3
Table 2: Post operative Heart rate (beats/min) of the studied subjects

Comparison of post-operative visual analogue score at regular intervals in comparison with baseline. The baseline value at 3o min postoperatively were 2.8 ± 1.2 in the gabapentin group and 4.9± 1.2 in the control group. Values at all intervals when compared with the baseline showed a statistically significant difference (p < 0.05). Table 4 & fig 4.
Figure 7
Table 4: Post operative visual analogue score in studied subjects

<table>
<thead>
<tr>
<th>Time</th>
<th>Study</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.8</td>
<td>4.9</td>
</tr>
<tr>
<td>60 min</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>90 min</td>
<td>2.5</td>
<td>4.6</td>
</tr>
<tr>
<td>120 min</td>
<td>2.7</td>
<td>4.9</td>
</tr>
<tr>
<td>3 hours</td>
<td>2.4</td>
<td>5.1</td>
</tr>
<tr>
<td>6 hours</td>
<td>2.6</td>
<td>5.2</td>
</tr>
<tr>
<td>8 hours</td>
<td>2.5</td>
<td>4.8</td>
</tr>
<tr>
<td>10 hours</td>
<td>2.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Figure 10
Table 6: Rescue Analgesic required in the studied subjects

<table>
<thead>
<tr>
<th>Time</th>
<th>Study</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>2.8</td>
<td>4.9</td>
<td>0.000</td>
</tr>
<tr>
<td>60 min</td>
<td>2.5</td>
<td>4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>90 min</td>
<td>2.5</td>
<td>4.6</td>
<td>0.002</td>
</tr>
<tr>
<td>120 min</td>
<td>2.7</td>
<td>4.9</td>
<td>0.003</td>
</tr>
<tr>
<td>3 hours</td>
<td>2.4</td>
<td>5.1</td>
<td>0.004</td>
</tr>
<tr>
<td>6 hours</td>
<td>2.6</td>
<td>5.2</td>
<td>0.005</td>
</tr>
<tr>
<td>8 hours</td>
<td>2.5</td>
<td>4.8</td>
<td>0.006</td>
</tr>
<tr>
<td>10 hours</td>
<td>2.5</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 9
Fig 4: Comparative postoperative visual analogue score in the studied subjects.

In group A, 17 patients (34%) required rescue antiemetic whereas in group B, 27 patients (54%) required rescue analgesic. Requirement for rescue analgesic in the two groups showed a statistically significant difference (0.044). Table 5

In group A, 17 patients (34%) required rescue antiemetic whereas in group B, 27 patients (54%) required rescue analgesic. Requirement for rescue analgesic in the two groups showed a statistically significant difference (0.044).

DISCUSSION
International association for study of Pain defines pain as “unpleasant sensation and an emotionally charged experience associated with actual or potential tissue damage or described in terms of such damage (11). Pain includes not only the perception of an uncomfortable stimulus but also the response to that perception (12). Pain intensity is the parameter most often monitored because it best reflects the degree of discomfort. Visual analogue scale (VAS) is the most commonly used to assess the pain intensity (13).

Gabapentin, an anticonvulsant has been shown to treat a variety of chronic pain conditions and has quiet recently been extended to acute pain management of postoperative pain. With more than 40 clinical trials evaluating the potential use of gabapentin for postoperative analgesia, preoperative analgesia, prevention of chronic postoperative pain, attenuation of haemodynamic response to laryngoscopy and intubation and prevention of postoperative nausea and vomiting etc.

Our results showed the mean duration of surgery in the gabapentin group was 62.8 ± 19.69 whereas in the placebo group it was 66.3 ± 18.72. The mean duration of anaesthesia in the placebo group was 74.8 ± 19.69 min whereas in the placebo group was 76.8 ± 18.72 min. the difference on comparison being insignificant.

Intraoperative monitoring of heart rate showed a significant difference from baseline between the two groups showing a significant increase at 15min and thereafter. Similarly other haemodynamic parameters as systolic blood pressure showed a significant difference between the two groups at 15 min. time intervals from baseline. The comparative difference in the systolic blood pressure between the two groups continued in the postoperative also for next 12 hours postoperatively. Comparing the intraoperative and postoperative diastolic blood pressure remained insignificant between the two groups with no significant change from baseline diastolic blood pressure.

The postoperative pain assessment was done by VAS at 30min intervals for first 2 hours, then at 1 hour interval in next 4 hours and finally at 2 hourly intervals for next 6 hours. The baseline level at 30 min postoperatively was 2.8 ± 1.2 in the gabapentin group and 4.9 ± 1.2 in the placebo group. 13(26%) patients in the gabapentin group required rescue analgesia medication (morphine) as compared to 30(60%) patients in the placebo group the difference being statistically significant.

The results of our study are comparable with Drik J Fredensborg BB et al 2002 (14) who observed the incidence of postoperative pain after radical mastectomy was
significantly lower in the gabapentin group (7 patients 24% (7/70)) as compared to 39 patients (58%) 39/70 in the placebo group needed rescue morphine analgesia in the postoperative period; gabapentin causing significant pain control and reduced morphine consumption postoperatively. Comparatively in our study 13(26%) in the gabapentin group and 30(60%) in the placebo group required analgesia.

Rachael K Seib, James E Paul et al 2002 (15) analysed the role of gabapentin as an analgesic. Their outcome based on the study of 8 placebo controlled randomised controlled trials and conducted a meta-analysis using primary outcome of pain scores, total analgesia consumption and side effects over a 24 hour period. In this study which is in agreement to our study patients who received gabapentin preoperatively reported significantly lower pain scores on a 10 point VAS scale and a lower opioid consumption with no difference in the incidence of side effects

CK Pandey et al in 2005 (16) studied 56 ASA I &II Patients randomly allocating to two groups to receive either gabapentin or placebo 2hours preoperatively. Fenatnlyl 2 mcg/kg was used as rescue analgesic. The study concluded that 300mg gabapentin significantly decreased postoperative pain in patients. The study was similar to our study. Similarly studies by Turan A, Memis et al 2006 (17) using gabapentin 1200mg 1 hour prior to surgery in patients undergoing ambulatory rhinoplasty or endoscopic sinus surgery showed an analgesia efficacy of gabapentin similar to our findings.

VK Grover et al in 2009 (18) evaluated the effects of a single dose of preoperative gabapentin for pain reduction and requirement of inj. Morphine after total mastectomy and axillary dissection and conclusively found that 60mg provide significant post-operative analgesia without side effects.

Our study is not consistent with the work of Radhakrishnan etal 2001 (19) a study designed to detect the influence of gabapentin premedication on morphine consumption, wherein 800mg gabapentin did not decrease morphine requirement or morphine side effects in patients undergoing lumbar laminectomy and discectomy.

A study in 2001 by M Werner, Perkins FM Holte K et al (20) done to examine the analgesic effects of gabapentin. Quatibitic sensory testing (QST) included pain ratings to thermal and mechanical stimuli (VAS) assessments of thermal and mechanical detection threshold and areas of secondary hyperalgesia, and they concluded that gabapentin has no analgesic effect in normal skin but may reduce primary mechanical alldynia in acute inflammation following thermal injury. These observations suggest a clinical potential of gabapentin in the treatment of postoperative pain.

In a major study forwarded by Ole Mathiesen in 2004 (21) in which quantitative analysis of combined data from similar procedures were prepared by collecting the weighted mean difference (WMD) of 24 hours cumulative opioid requirements and the WMD for VAS pain( early 6 hours) and late (24hours) postoperatively between study groups. 23 trials with 1529 patients were included. 12 of 16 studies reported significant reduction in 24 hour opioid requirement and 5 trials in abdominal hysterectomy showed a significant reduction in morphine consumption and in early pain scores at rest and during ambulation and concluded that perioperative use of gabapentin has a significant 24 hour opioid sparing effect. This major study is in complete congruence with our findings.

CONCLUSION

We conclude that prophylactic use of gabapentin before mastectomy reduces the incidence of postoperative pain, reduces postoperative morphine consumption and a significant degree of analgesia is achieved.

References
11. IASP- International Association for the study of pain,
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