

ORIGINAL RESEARCH

PAIN MANAGEMENT

Preventive analgesia with oral tramadol and pregabalin for post-operative pain in breast surgical patients

Ali Usman¹, Syed Raza Mehdi², Asma Ashraf Khan³

Authors affiliations:

1. Ali Usman, Fellow Anesthesia, Shaukat Khanum Memorial Cancer Hospital & Research Center, 7-A, M.A Johar Town, Lahore, Pakistan; E-mail: draliusman8166@gmail.com
2. Syed Raza Mehdi, Consultant Anesthesia, Shaukat Khanum Memorial Cancer Hospital & Research Center, 7-A, M.A Johar Town, Lahore, Pakistan; E-mail: razamehdi@skm.org.pk
3. Asma Ashraf Khan, Consultant Anesthesia, Shaukat Khanum Memorial Cancer Hospital & Research Center, 7-A, M.A Johar Town, Lahore, Pakistan; E-mail: asmaashraf@skm.org.pk

Correspondence: Dr. Ali Usman, FCPS, FCA; E-mail: draliusman8166@gmail.com; Phone: 03320681667

ABSTRACT

Background & objective: Preventive analgesia is implied before the actual surgical insult occurs and it is aimed to reduce the neuro-humoral changes associated with surgical induced pain. Different methods have been used by the anesthesiologists for this purpose. We studied the effect of pre-emptive oral tramadol 50 mg and pregabalin 100 mg on post-operative pain, the requirement of rescue analgesics and the stay in post-anesthesia care unit (PACU) in breast cancer surgery patients.

Methodology: A randomized double blinded, placebo-controlled trial, was conducted in the Department of Anesthesia, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore (Pakistan) after ethical approval by the hospital Scientific Review Committee and Institutional Review Board. A total of 30 patients, undergoing breast cancer surgery, were enrolled and randomly divided into two groups. Group A (study group) patients were given tramadol 50 mg and pregabalin 100 mg orally, and Group B (control group) received two soda mint tablets orally 30 min prior to induction of anesthesia. Standard monitoring was done and routine general anesthesia was administered with intubation. After recovery, Visual Analog Scale (VAS) scores and time to rescue analgesia, total morphine consumption, were recorded. Data was analyzed using SPSS v.20. $P < 0.05$ was considered significant.

Results: The mean ages in Group A and B were 36.67 ± 9.50 y and 41.80 ± 12.43 y ($P = 0.236$). The differences in intra-operative morphine and rescue morphine use in both groups were not significant ($P = 0.139$ and 0.293 , The rescue analgesic use and VAS scores in PACU were significantly different in both groups ($P = 0.005$ and $P = 0.022$, respectively). Total PACU stay in Group A was 79.33 ± 26.31 min and in Group B was 96.67 ± 34.98 min ($P = 0.281$). Tramadol use in the ward was not statistically equivalent ($P = 0.300$). Mean post-operative rescue morphine was 0.2 ± 0.775 mg/kg in control group as compared to placebo group was 1.4 ± 1.682 mg/kg, which was statistically significant ($P = 0.02$). VAS scores in PACU in both groups showed statistically differences, e.g., 1.33 ± 1.1 vs 2.70 ± 1.60 ($P = 0.01$). PACU stay time was also higher in the control group.

Conclusion: The use of pre-emptive analgesia with oral tramadol 50 mg and pregabalin 100 mg 30 min before the surgery can reduce the requirement of peri operative opioid use, achieve better pain control and early recovery.

Abbreviations: BMI- Basal Metabolic Rate; PACU- Post-Anesthesia Care Unit; PONV- Postoperative Nausea and Vomiting; VAS- Visual Analog Scale

Key words: Analgesia, Preventive; Cancer Surgery; Opioids; Post-Anesthesia Care Unit; Pregabalin; Tramadol

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1. INTRODUCTION

Preventive analgesia is not a novel concept but in the recent times it has carved a significant place for itself in the management of acute and chronic pain.¹ Preventive analgesia requires a very meticulous calculation of dosage and timing of the medicine to control the pain and the stress response associated with it. In 1983 Woolf was the first one to describe the concept of preventive analgesia to reduce the intensity of postoperative pain. In his experimental studies he established a relation of central component of post-injury pain hypersensitivity.² This was reinforced by the experimental data that various anti-nociceptive techniques were more effective in reducing the post-injury central sensitization phenomena when administered before injury as compared to when they were given after the surgical insult.³ These findings were then taken into clinical testing of the hypothesis.⁴ Different pharmacological and non-pharmacological methods have been used and the concept of preventive analgesia revolves around blocking as many receptors before the surgical stimulus. It not only reduces the acute pain it also prevents the development of chronic pain. Proper management of pain has multifaceted advantages as it results in early mobilization, increased patient satisfaction, reduced hospitalization period and costs.

Tramadol is a weak opioid that inhibits the reuptake of noradrenaline and serotonin, and its metabolite has affinity for opioid μ -receptors. Pharmacokinetics of the drug are also favorable as it offers high bio-availability, with similar patterns after enteral or parenteral administration. Pregabalin is an antiepileptic drug that acts on calcium channels in the CNS and used for neuropathic pain and preventing chronic post-surgical pain.

Optimal pain control is even more important in breast cancer surgery as it is one of the surgeries associated with higher rates of chronic post-surgical pain. Different modalities are used to mitigate the pain including intravenous analgesic agents and local anesthetic agents. We conducted this study to determine the efficacy of the use of tramadol and pregabalin as preventive analgesia and reduction of opioid use in intra-operative as well as post-operative period.

2. METHODOLOGY

It was a randomized double blinded, placebo-controlled trial, conducted in the Department of Anesthesia, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore (Pakistan) after ethical approval by the hospital Scientific Review Committee and Institutional Review Board. Non-probability consecutive sampling was done and all patients, undergoing breast surgery, of ages between 18 and 65 y,

American Society of Anesthesiologists (ASA) status 1 and 2, were included. Informed written consent was obtained. Thirty patients in total were recruited. Any patient with known allergy to either of the medicines or who were taking beta blockers, were excluded. The patients were randomly divided into two groups using an online software. Patients of the study group were given tab tramadol 50 mg and pregabalin 100 mg, and patients in placebo group were given 2 soda mint tablets per oram 30 min prior to induction of anesthesia. Both the patients and the anesthetist were kept unaware of the group of the patient. All the patients received ASA standard monitoring and induction of general anesthesia with propofol 2-4 mg/kg and atracurium 0.4-0.5 mg/kg. Airway was secured with a supra-glottic device. Anesthesia was maintained with sevoflurane of 1.3 MAC in oxygen and air mixture.

All the patients received 15 mg/kg paracetamol IV and 1 mg/kg diclofenac IV, along with infiltration of 20 ml of 0.25% bupivacaine at the surgical site prior to the incision. Intra-operative rescue analgesia was given in the form of incremental doses of 2 mg morphine by the anesthetist if there was more than 20% rise in either blood pressure or heart rate from the base line.

Visual analogue scale (VAS) score was used to record pain in post anesthesia care unit (PACU). Time to the first rescue analgesia was noted. Patients were discharged from the PACU once they fulfilled the criteria. Total analgesic drugs consumed in the subsequent 24 h were recorded on the approved proforma. Data was analyzed using SPSS v.20. $P < 0.05$ was considered significant.

3. RESULTS

Thirty (30) patients were included in the study. The demographic data is given in Table 1. Average duration of the surgery was equivalent in both groups ($P = 0.411$). Intra-operative morphine and rescue morphine used in both groups were equivalent ($P = 0.139$ and 0.293 respectively). Rescue analgesia and VAS scores and tramadol used in PACU were significantly different in both groups ($P = 0.005$, 0.022 , and 0.012 respectively).

Total PACU stay by patients of Group A was 79.33 ± 26.31 min and in Group B was 96.67 ± 34.98 min, ($P = 0.281$). The difference between the tramadol use in the ward was statistically not significant with $P = 0.300$ (Table 1).

The use of diclofenac, paracetamol, and dexamethasone, was equivalent in both groups; but ondansetron and local anesthetic for infiltration were used significantly more in Group B (Table 2). The number of patients complaining

Table 1: Demographic and study statistics

Variables	Group A	Group B	P-value
Age (y)	36.67 ± 9.50	41.80 ± 12.43	0.236
BMI (kg/m ²)	27.04 ± 4.72	26.51 ± 5.47	0.465
Duration of surgery (min)	81.00 ± 28.23	82.00 ± 31.39	0.411
Intra operative morphine (mg/kg)	1.20 ± 1.70	1.87 ± 2.36	0.139
Rescue morphine (mg/kg)	00.20 ± 0.78	01.40 ± 1.68	0.293
Rescue analgesia need [n (%)]	1(6.67)	8(53.33)	0.005
VAS Scores	01.33 ± 2.67	02.67 ± 1.59	0.022
Total PACU stay (min)	79.33 ± 26.31	96.67 ± 34.98	0.281
Tramadol in PACU (mg/kg)	06.67 ± 25.82	23.33 ± 41.69	0.012
Tramadol in ward (mg/kg)	30.00 ± 45.52	43.33 ± 49.52	0.300

Data given as mean ± SD; P < 0.05 was considered significant

Table 2: Comparison of different drugs used

Variables	Group A	Group B	p-value
Diclofenac	70.67 ± 8.84	70.67 ± 12.37	0.293
Paracetamol	953.33 ± 94.54	953.33 ± 89.58	0.864
Dexamethasone	4.53 ± 2.07	5.60 ± 2.53	0.077
Ondansetron	4.00 ± 0.00	4.33 ± 0.90	0.002*
LA used	12.33 ± 417	14.67 ± 5.16	0.011*

Data given as mean ± SD; P < 0.05 was considered significant

Table 3: Comparative VAS Scores in the groups

VAS Score	Group A	Group B	P-value
1	13 (86.66)	06 (40.00)	0.05
2	01 (6.67)	01 (6.67)	
3	0 (0.00)	02 (13.33)	
4	0 (0.00)	04 (26.67)	
5	01 (6.67)	02 (13.33)	

Data given as n (%); P < 0.05 was considered significant

of mild to moderate pain according to VAS score, were significantly more in Group B compared to Group A (P = 0.002 and 0.011) as shown in Table 3.

4. DISCUSSION

Postoperative pain management is considered as one of the most challenging issues for the anesthetists and it has an integral part in the optimum healthcare provision to the patients. Surgical trauma not only causes the biochemical changes at the surgical site but also induces hyperalgesia in the central nervous system which results

in the development of chronic post-surgical pain. Acute post-surgical pain often requires the use of different pharmacological agents among which non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are the most commonly used drugs, but the later are associated with significant risk of nausea, vomiting and delayed recovery.

The mean age of patients in our study was 39 ± 11 y, enrolled for breast surgery. A retrospective research conducted by Alabdulkarim et al. (2018), enrolled 224 patients underwent surgery for breast cancer at King Saud University Medical City, Riyadh, with overall mean age of

48.8 ± 12.2 y.⁵

The current study showed that mean BMI in Group A was 27.04 ± 4.72 and in Group B was 26.51 ± 5.47. A study conducted by Konishi et al. (2020), included 108 patients undergoing breast cancer surgery. They found an association of BMI with postoperative complications, length of stay, and hospitalization costs, and a linear association with duration of anesthesia.⁶

Average duration of the surgery was equivalent in both groups (P = 0.411). Intra-operative morphine and rescue morphine was also equivalent in both groups, the difference being not significant (P = 0.139 and 0.293 respectively).

There is a growing concern of immunomodulation and metastasis of the cancer after use of opioids as shown by Afsharimani et al.⁷ On the contrary, recent studies have reported association of intraoperative opioids with improved recurrence-free survival in triple-negative breast cancer.⁸

The current study showed that the need for rescue analgesia, VAS scores and tramadol use in PACU were higher in Group B. The total PACU stay for Group A was less compared to Group B, but the difference was

insignificant ($P = 0.281$). Tramadol use in the ward was statistically equivalent in the two groups ($P = 0.300$). Research conducted by Kumar et al. observed that preventive analgesia with tramadol and pregabalin before lumbar laminectomy significantly reduced the post op pain scores and the rescue analgesia.⁹ A meta-analysis by Chang et al. also demonstrated the reduction in pain scores and decreased use of post-operative opioid consumption after breast surgery, it also resulted in decreased incident of chronic post-surgical pain.¹⁰ In one study by Trujilo-Estevés et al. pregabalin was prescribed for 72 hours before the planned surgery and pain score was recorded after laparoscopic cholecystectomy. The consensus still lacks regarding the dose and duration of preventive analgesia to get the maximum benefit with minimal side effects but a linear relation has been observed between the increasing dose of pregabalin and reduction in pain scores.¹¹

One meta-analysis by David L et al. found that pregabalin not only reduced post-operative pain but also decreased opioid consumption and their side effects such as sedation, constipation, respiratory depression, urinary retention and vomiting.¹² Other post-operative complications were also noted in a study by Kohli et al. and they concluded that pre-operative administration of single dose pregabalin was associated with reduced blood pressure, heartrate and anxiety level.¹¹

In our study only two patients complained of postoperative nausea and vomiting (PONV), both from the placebo group, this could partly be explained by the fact that control group had lower consumption of rescue analgesia as compared to the placebo group and partly by the anti-emetic effect of pregabalin as reported in previous studies.¹³⁻¹⁶ But the results regarding PONV in our study are inconclusive as the sample size of our study was small. In a meta-analysis by Hu J et al. about effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain they established a non-linear relation between the dose of preventive analgesia and post op opioid consumption.¹⁷ In another study which was done by Fahim et al., patients who were planned for herniorrhaphy and were given preventive tramadol, there was reduction in post-op consumption of opioid and visual analogue scores.¹⁸

In our study, a statistically significant reduction in rescue analgesia and visual analogue scores of pain was consistent with previous studies. Additionally, patients in the control group had to stay in the PACU for a shorter time compared to the patients in the placebo group. In developing countries, where opioid availability is an issue, these easily available weak and non-opioid analgesic options can offer an alternative form of pain relief, additionally avoiding the unwanted effects of opioids.

5. LIMITATIONS

Sample size of our study was small and the secondary outcomes of our study, post op PONV and total PACU stay time were not conclusive. Moreover, the use of tramadol, a weak opioid, could have contributed more to the analgesia of the control group. A subjective assessment of patient satisfaction could also have been done. Further larger, randomized control trials are still required to bridge these gaps.

6. CONCLUSION

Administering preventive analgesia in patients planned for surgery can help in reduction of peri operative opioid dosage and it ensures better pain control. Additionally, the side effects of opioids can also be avoided.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

9. Authors' contribution

AU: Conduct of study, data collection and manuscript writing

SRM: Concept, manuscript editing, data collection

AAK: concept, manuscript editing

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