ORIGINAL ARTICLE

Pre-emptive Analgesic Effect of Gabapentin in comparison with Diclofenac Sodium in patients undergoing abdominal surgeries

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ABSTRACT

Background: Pain after abdominal surgery not only distresses the patient but also results in inadequate respiratory efforts and cough reflex. So pain relief in these surgeries bears more significance than mere patient comfort. Acute postoperative pain can lead to significant morbidity and mortality. Preemptive analgesic given before an operation provides early analgesia, even before the initial exposure to a noxious stimulus provides effective postoperative pain relief. In developed countries pre emptive analgesia is practiced routinely as part of well-defined protocol.
Aim: To compare the efficacy of Gabapentin and Diclofenac Sodium as pre-emptive analgesic, for post-operative pain relief in patients undergoing abdominal surgeries.
Methods: This randomized clinical trial was conducted at Department of Anesthesia King Edward Medical University/Mayo Hospital Lahore. Total 140 patients were included in the study and randomly divided into two groups i.e., Gabapentien Group (Group A) and Diclofenac Sodium Group (Group B), 70 patients in each group. Patients in Group A were given cap. Gabapentin 600mg and in Group B tab. Diclofenac Sodium 100mg along with a sip of water one hour before shifting to operation theatre . All patients were anesthetized with standard general anesthesia protocol with same induction agents. After completion of surgery patients were shifted to recovery area, where pain was measured at 0 and 30minutes then patients were shifted to ward and observed there for 12hours. In ward pain was measured by VAS half hourly for 1st hour and then for 120 (2 hours) 240 (4 hours), 360 (6 hours) and 720(12 hours) minutes after the surgery.
Results: Mean age of patients in Group-A and in Group-B was 42.18±12.69 and 41.42±10.41 years. In Group-A there were 34 male and 36 female patients while in Group-B there were 37 male and 33 female patients. In this study pain score at 0 and 30th minutes was same in both treatment groups. However at 60th minute patients in Group-A had better pain control as compare to Group-B at this point, 77% patients in Group-A and 67% in Group-B had no pain. (P-value at 60th Min=0.032). At 120th minute 70% patients in Group-A and 64% in Group-B did not experience any pain. From 240th minute till 720th minute pain control of patients was significantly better in Group-A as compared to Group-B. While literature searches showed none of the study has compared Diclofenac Sodium with Gabapentin as pre-emptive analgesia especially in patients undergoing abdominal surgeries.
Conclusion: The use of a single oral dose of Gabapentin is significantly effective as compared to Diclofenac Sodium when used as Pre-emptive analgesic for post-operative pain relief. The effect not only lasts longer but it also reduces the need for rescue analgesia.
Keywords: Gabapentin, Diclofenac Sodium, Pre-emptive analgesia, Post-operative pain relief

INTRODUCTION

Pain is a common and unpleasant human perception that provokes both fear and anxiety which may last for a life time[1]. Pain ''an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage''[2].

Pain control is an important phenomenon; the pain which is not relieved during and after surgery can interfere with sleep and physical functioning and can cause worst effects on patient's well-being. Uncontrolled pain may cause hypertension, myocardial ischemia, arrhythmias, respiratory impairment, and ileus[3].

Preemptive analgesia is defined as a pain treatment that is initiated before surgery in order to inhibit the establishment of central sensitization evoked by inflammatory damage occurring during operation and in early post-op period. The focus of pre-emptive analgesia is not the relative timing of intervention but on decreasing the impact of peripheral nociceptive barrage associated with noxious pre-operative, intra-operative or post-operative stimuli[4].

Effective post-op pain control is very important and is achieved by preventing initial neural cascade which leads to hypersensitivity produced by noxious stimuli and preventing central sensitization. Thus it prevents typically painless sensations which may be experienced as pain allodynia[5].

Different agents can be used for this purpose. EL Sonabaty et al, found a combination of bupivacaine and ketamine for local infiltration of peritonsillar area to provide effective analgesia and better parental satisfaction in children under going adenotonsillectomy[4].

Biyik et al, studied the effect of Gabapentin and Diclofenac on pain and opioid consumption after sternotomy[6]. Various analgesic agents have been used for postoperative pain with different side effects like respiratory depression, nausea, constipation and agitation. Some agents like NSAIDs interfere with platelet aggregation which harms the gastric mucosa and prolong bleeding time[7]. These are the limiting factors for the use of NSAIDs as pre-emptive analgesics.

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Pre-treatment with Gabapentin decreases acute pain after various surgical procedures and can inhibit the development of hyperalgesia. Gabapentin has a selective effect on the nociceptive process including central sensitization[8]. Gabapentin is believed to exert its analgesic effect by binding to pre-synaptic voltage gated Ca^{2+} channels and inhibits the release of excitatory neurotransmitters[9]. Gabapentin also decreases central sensitization by reducing hyper excitability of dorsal horn neurons produce by tissue damage. These anti allodynics and anti hyperalgesic properties may therefore also be useful in acute post-op pain control[10]. Pathak L found that pre-medication with Gabapentin was effective in reducing pre-op anxiety as well as post-op pain[11].

Gabapentin a newer agent has been found effective for chronic pain management, is now used for postoperative pain relief. Literature search show that none of the study has compared diclofenac sodium with gabapentin as pre-emptive analgesic especially in abdominal surgery. Most of the studies have done gabapentin comparison with other drugs or with placebo.

The study aims to compare Gabapentin with diclofenac sodium for post-op pain relief in patients undergoing abdominal surgeries.

MATERIAL AND METHODS

This Randomized controlled trial was conducted in Department of Anesthesia King Edward Medical University/ Mayo Hospital, Lahore. Total 140 patients were included in the study and randomly divided into two groups i.e., Gabapentien Group (Group A) and Diclofenac Sodium Group (Group B). Each group contained 70 patients.90% power of test with 10% level of significance were taken to calculate the sample size. Patients of ASA I and II, ages 18 – 60 years, either gender, scheduled for elective abdominal surgery were included in this study. Patients with history of allergy to Gabapentin or NSAID, stomach bleeding and coagulation disorders and Epilepsy were excluded from the study. Moreover drug abusers and patients on regular long term analgesics and corticosteroids were also omitted.

Data collection procedure: This study was conducted after approval of ethical committee of hospital, IRB of KEMU. After the consent of patient, basic and demographical (age, gender etc.) information was obtained. All the patients undergoing abdominal surgery, admitted through OPD (fulfilling inclusion criteria), were randomly divided into two groups i.e., group A (Gabapentin)and group B (Diclofenac Sodium)with 70 patients in each group. Patients in group A were given cap. Gabapentin 600mg and in group B tab. Diclofenac sodium 100mg along with sip of water one hour before shifting to operation theatre. After shifting to operation theatre all the standards of monitoring were followed i.e. standard one and standard two monitoring was instituted to all patients. General anesthesia was induced with IV Propofol 2mg/kg followed by inj atracurium 0.5mg/kg to facilitate endotracheal intubation IV Nalbufen 0.1mg/kg bolus was given for intra operative analgesia. Anesthesia was maintained with 50% oxygen and 50% nitrous oxide isoflurane 2 volume% and intermittent 10mg bolus of inj atracurium as per requirement. Intra operative hemodynamic parameters were recorded with the 5 minutes interval with the total blood loss, length of anesthesia, length of surgery and time to tracheal extrubation. Intravenous 4mg odensteron was given to every patient 15 minute before end of surgery.

Isoflurane was discontinued at the beginning of skin closure. At the end of surgery after initiation of spontaneous respiration, reversal of neuromuscular blockage was done with IV neostigmine 0.05mg/kg and glycopyrolate 0.01mg/kg. After patient started obeying commands patient was extrubated then patient was shifted to recovery area adjacent to Operation Theater. Where pain was measured at 0 and 30minutes then patient was shifted to ward and observed for 12hours.In ward pain was measured by VAS half hourly for 1st hour and then for 2 hourly 120,240,360 and 720minutes after the surgery. Time interval between admission and patients first requirement for analgesic (i.e. time first analgesic demand) was noted. Along with the pain VAS, HR, BP, SpO2 and side effects like nausea, vomiting, headache, sedation, and respiratory depression were observed post operatively. Side effects observed were treated whenever indicated like respiratory depression or SpO2 <90% was treated with oxygen supplementation.

Data analysis procedure: The data was analyzed in the statistical program SPSS 20.0 version. The results for quantitative data like age and pain (VAS scale) were expressed by mean ± standard deviation. Qualitative data (like, gender) was presented in form of frequency and percentages (%) Chi-square and fisher's exact test was applied to see any significant difference between independent variables and outcome variable. A level of 5% (p-value≤ 0.05) was used for significant testing and association.

RESULTS

Mean age of patients in Group-A and in Group-B was 42.18±12.69 and 41.42±10.41 years. *(Table-1)*

In Group-A there were 34 male and 36 female patients while in Group-B there were 37 male and 33 female patients included in this study.*(Graph-1)*

From 0 minute till 30th minute pain score was statistically same in both treatment groups. [0th-Min=0.653, 30th Min=0.653]. At 60th minute pain score was significantly different in both treatment groups. Pain score of patients in Group-A was more stable as that of Group-B patients. [60th-Min (p-value)=0.032]) At 120th minute 70% patients in Group-A and 64% in Group-B did not experienced any pain. [120th-Min (p-value)=0.7259] From this point forward means from 240th till 720th minute pain status was significant better as that of Group-B. [240th-Min (p-value)=0.041, 360th-Min (p-value)=0.048 & 720th-Min (p-value)=0.031]*(Table-2)*

Table 1: Descriptive statistics for age(years) in treatment groups

	Group-A	Group-B
N	70	70
Mean	42.18	41.42
SD	12.69	10.41
Minimum	28.00	18.00
Maximum	60.00	60.00

Group A =Gabapentin Group B=Diclofenac Sodium

Graph-1: Gender Distribution in treatment groups

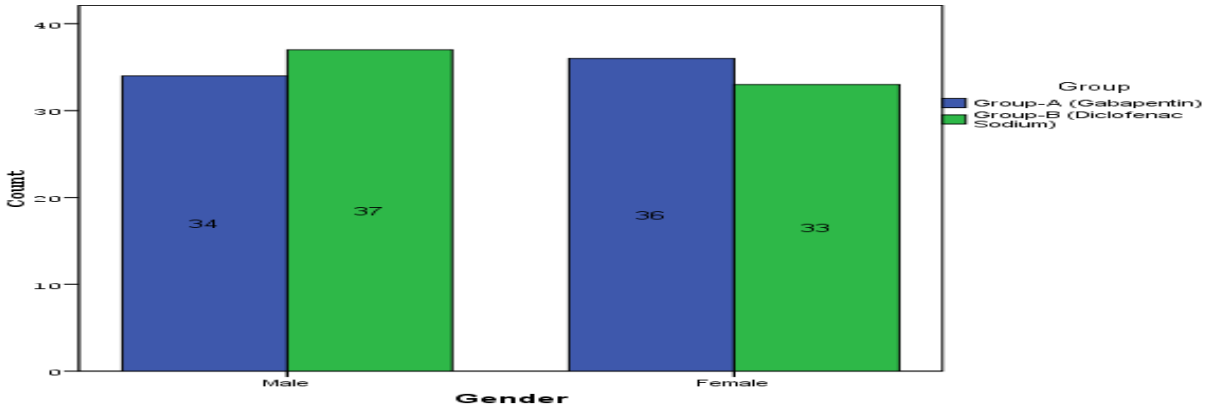

Table-2: Severity of pain in treatment groups during follow up time period

Pain Status	0-Min		30-Min		60-Min		120-Min		240-Min		360-Min		720-Min	
	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB	GroupA	GroupB
No Pain	59(84%)	57(81%)	59(84%)	57(81%)	54(77%)	47(67%)	49(70%)	45(64%)	47(67%)	34(49%)	44(63%)	30(43%)	41(59%)	29(41%)
Mild	11(16%)	13(19%)	11(16%)	13(19%)	14(20%)	12(17%)	15(21%)	19(27%)	12(17%)	24(34%)	8(11%)	20(29%)	13(19%)	18(26%)
Moderate	0(0%)	0(0%)	0(0%)	0(0%)	2(3%)	11(16%)	6(9%)	6(9%)	6(9%)	3(4%)	10(14%)	11(16%)	12(17%)	9(13%)
Severe	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	5(7%)	9(13%)	8(11%)	9(13%)	4(6%)	14(20%)
Total	70	70	70	70	70	70	70	70	70	70	70	70	70	70
P value[a]	0.653		0.653		0.032*		0.7259		0.041*		0.048*		0.031*	

Note: (a) p-value was calculated by using Chi-Square Test, (*) p-value<0.05 (Significant)

DISCUSSION

The concept of pre-emptive analgesia has gained popularity and previous researches have shown the value of preemptive analgesic effect of some drugs like opioids, local anesthetics and nonsteroidal anti-inflammatory drugs. Surgeries including skin cuts may cause initial sensitization. These observations on the origin and the perception of pain lead to the concept that the analgesia given before a noxious stimulus is effective as the same dose given later[12,13].

Preemptive analgesic efficacy of gabapentin has been demonstrated earlier in a few studies[8,14]. Lamotrigine had demonstrated analgesic effects in animal models of neuropathic pain including painful diabetic neuropathy and gabapentin-resistant neuropathic pain. They are also reported to be effective in several forms of neuropathic pain in clinical studies[15,16].

Dirks study linked data from animal models and clinical trials for chronic pain induced by the effect of gabapentin on acute nociception and experimental cutaneous hyperalgesia in healthy volunteers indicated that Gabapentin decreases established cutaneous sensitization[17].

This class of drugs operate over three main mechanisms, namely, enhancement of the transmission of gamma-aminobutyric acid (GABA), reducing glutamate-mediated excitatory transmission and blocking of voltage-dependent ion channels. The new generation of antiepileptic drugs such as, topiramate, lamotrigine, and gabapentin, are effective in animal models of neuropathic pain by blocking voltage dependent ion channels[18,19].

Although these novel antiepileptic agents share the same mechanism for their efficacy in neuropathic pain, preemptive use of novel antiepileptics such as topiramate, lamotrigine, and gabapentin is strongly recommended to prevent CNS sensitization leading to pain amplification by the incisional and inflammatory injuries occurring during surgery. Immediate postoperative pain may be reduced and the development of chronic pain may be prevented with effective use of preemptive analgesic[20].

In this study postoperative pain score of patients at 0 and 30th minutes was statistically same in both treatment groups. However at 60th minute patients in Group-A had better pain control as that of Group-B. Seventy seven percent patients in Group A and 67% in group B had no pain. (p-value (60th Min=0.032) From 240th minute till 720th minute pain scores were significantly lower in Group-A as that of Group-B. Previous literature research did not show comparison of diclofenac sodium with gabapentin as pre-emptive analgesic especially in patients undergoing abdominal surgeries. Most of the studies have done gabapentin comparison with other drugs or mostly with placebo focusing on postoperative pain status and analgesia requirement.

Harshel G. Parikh studied the effect of oral gabapentin used as preemptive analgesia to decrease postoperative pain in patients of abdominal surgical procedure under general anesthesia. The VAS scores at 0, 2, 4, 6, 12, and 24 h were 1.9 vs. 2.4 (P=0.002), 2.3 vs. 3.0 (P=0.000), 3.2 vs. 3.7 (P=0.006), 2.9 vs. 4.4 (P=0.000), 3.6 vs. 4.6 (P=0.000), and 3.7 vs.4.6 (P=0.000), respectively. Numbers of patients requiring rescue analgesia with placebo were 3 vs. 14 (P=0.004)[8]. The results of our study is consistent with that reported by Harshel G. Parikh both showing better pain control with Gabapentin as that of Diclofenac Sodium in patients undergoing abdominal surgeries.

Turan et al, also showed that Gabapentin administered one hour prior to operation significantly decreased the post-operative pain scores and Tramadol requirement in patients of total abdominal hysterectomy[21]. Turan's study results are comparable with the results of our

research showing the effectiveness of Gabapentin in better pain control when used as a preemptive analgesic.

Study results by Chetna A. Jadeja are also consistent with the results of our study. He also reported statistically significant less pain scores at all times in Gabapentin group as compared to placebo group. He demonstrated that pre-emptive oral Gabapentin significantly reduced tramadol consumption until 24 hours post-operatively[22]. The only difference was that we compared Gabapentin with Diclofenac Sodium.

Picazo A et al in 2006 showed, that low dose of Gabapentin-Diclofenac synergistic combination may represent a therapeutic benefit in the clinical treatment of inflammatory pain[23]. This is in accordance with our study, the only difference was that we used the drugs separately.

On the other hand, post-operative analgesic effect of Gabapentin has been controversial some times. In the review of Kissin, it has been stated that pre-operative Gabapentin has not shown significant reduction in pain score after mastectomy[14,25] in contrast with the findings of our study.

Mahdi Panah Khahi, Shaqayeq Marashi in 2012 evaluated that no significant analgesic efficacy of oral gabapentin 300 mg immediately after tibial internal fixation surgery under spinal anesthesia at 2, 12 and 24 hours postoperatively. They compared gabapentin with placebo[11].

Our study is limited by the facts that the pain score was monitored only 12 h postoperatively missing out a possible longer duration of effect of preoperative Gabapentin. Another limitation of our study was that we evaluated only single dose of 600mg Gabapentin. A dose-ranging study is warranted to determine the lowest dose with maximum efficacy for postoperative analgesia in abdominal surgeries. Future investigations for determining the dose-response relationship will be required.

Thus, it can be said that preemptive use of oral Gabapentin 600 mg effectively reduces the post-operative pain and the analgesic requirement for the patients.

CONCLUSION

Results of this study demonstrated that use of a single oral dose of Gabapentin as Pre-emptive analgesic in patients undergoing abdominal surgeries is effective for post-operative pain control, the effect of this drug not only lasts longer but it also reduces the need for rescue analgesic.

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