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Research Article

Gabapentin plus celecoxib as preemptive analgesia in complex spine surgery for improving perioperative patient anxiety and satisfaction, Is it effective?

randomized double-blind controlled clinical trial

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Abstract

Background: Preemptive administration of analgesic medication is more effective than medication given after the onset of the painful stimulus. This study aimed to evaluate the effect of gabapentin plus celecoxib as pre-emptive multimodal analgesia on anxiety score, patient satisfaction score, visual analog scale (VAS), and analgesic requirement. **Methods:** This randomized double-blind controlled clinical trial was carried out at Minia University Hospital. Fifty adult patients ASA I and II undergoing elective complex spine surgery. Patients were divided into two groups, 25 patients in each group; group A received 300mg gabapentin + 200mg celecoxib 2 hours before surgery; group B (placebo) received two placebo capsules orally 2 hours before surgery. Anxiety score, patient satisfaction, VAS, and perioperative analgesic requirements were assessed**. Results:** anxiety score was significantly lower in the study group compared with a control group (1.2±0.5) versus (3.8±1.7), respectively. The time for the first request for postoperative analgesia showed statistically highly significant longer duration in the study group compared to the control group, and the total dose of fentanyl required during the first 24 h post-operatively showed highly statistically significantly lower values in the study group compared to control group ($P < 0.0001$). There was a significant difference between the study and control groups in patient satisfaction and VAS ($p=<0.0001$ and $p=<0.001$) respectively. **Conclusion:** Preemptive administration of multimodal analgesia as a combination of gabapentin 300mg plus celecoxib 200mg 2hr preoperative in the patients undergoing complex spine surgery provided lower anxiety, analgesic requirement, and led to a high patient satisfaction score.

Keywords: Preemptive analgesia, preoperative anxiety, Satisfaction, analgesic requirement

Introduction

The global increase in the incidence of low back pain has increased the number of spine surgeries being performed worldwide. The main aim of all surgeons is to improve stratification and better functional outcomes in standard spine procedures. The quality of surgical procedures alone does not contribute to satisfactory results.

Postoperative experience has a vital role in recovery and inadequate postoperative pain management following spine surgery can cause many medical complications such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and poor wound healing, also contributing to patient dissatisfaction and poor functional outcomes. So, adequate postoperative pain management

allows early ambulation, reduces hospital length of stay, and improves the quality of life. [1]

Many therapeutic modalities ranging from nonsteroidal anti-inflammatory drugs (NSAIDs) to systemic opioids, acetaminophen, patient-controlled opioid analgesia, and tramadol have been used also for postoperative pain management[2]. However, NSAIDs increase the occurrence of bleeding, opioids increase the risk of nausea, vomiting, and respiratory depression, also, patient-controlled analgesia always provides inadequate analgesia for movement. So, more opioids are required for rescue analgesia [3].

Gabapentin and pregabalin were effective in neuropathic pain control as postsurgical pain. Some research showed that oral celecoxib reduced postsurgical pain (effective as 600 mg aspirin or 1000 mg paracetamol). The use of 400 mg oral celecoxib can significantly reduce post-operative pain as a study on patients undergoing spinal surgery showed that [4]

Multimodal analgesia means the use of analgesic adjuncts with different mechanisms of action to increase postoperative pain management. It is a good choice for relieving postoperative pain with minimum side effects[5] and when it includes prophylactic administration of selective cyclooxygenase-2 (COX-2) inhibitors in different doses, it can improve postoperative pain and reduce opioid analgesic consumption in patients who underwent laminectomy [6]

Preemptive analgesia (PA) usually includes medications that are easy to administer with short onsets of action and have an adverse effect profile that will not compromise the planned surgical procedure. It may include NSAIDs, COX-2 inhibitors, pregabalin, gabapentin, and acetaminophen. The medications are administered 1 to 2 hours before incision[7]. Preemptive analgesia is an important part of multimodal analgesia [5].

Experimental evidence shows that it was possible and preferable to prevent and pre-empt the neurophysiological and biochemical consequences of noxious input to the CNS rather than to begin treatment when these consequences are already established. So, prevention of postoperative pain may be more effective than treatment [8]

Aim of the work

The primary goals were to evaluate the effect of a combination of gabapentin plus celecoxib as pre-emptive multimodal analgesia on, preoperative anxiety score and postoperative patient satisfaction score. The secondary goal is to assess pain alleviation through the Visual Analog scale and perioperative analgesic requirement.

Patients and Methods

Study design:

This randomized double-blind controlled clinical trial was carried out at Minia University Hospital from November 2017 to December 2018.

patient sampling:

After approval of the ethics committee of Minia University Faculty of Medicine, 50 patients aged between 20-60 years old ASA I and II patients scheduled to undergo elective posterior approach complex spin fixation surgery were enrolled in the study (fig,1). Neurosurgeons and anesthesiologists were the same in all patients. Informed written consent was obtained from each patient.

Patients were divided into two groups. In each group, there were 25 patients: group A received 300mg gabapentin + 200mg celecoxib 2 hours before surgery, and group B (placebo) received two placebo capsules orally 2 hours before surgery.

Sampling with a sealed envelopes technique and coding was done. The coding and sealed envelopes technique was prepared by a nurse who was not participating in the study. The patients with drug abuse, a history of allergic reaction to any of the study drugs, on non-steroidal anti-inflammatory analgesics, pregnancy, cardiovascular, metabolic, respiratory, peptic ulcer and renal failure, or coagulation abnormalities were excluded from the study.

Sample size calculation:
The required sample size was calculated using the G*Power 3.1.9.2 software. Based on a priori analysis for t-test difference between two independent means according to data obtained from a pilot study which reported the mean time of 1st analgesia in each group. With a medium effect size of 0.25, a significance level of 0.05, and a power of 0.80, the projected required sample size was calculated to be 50.

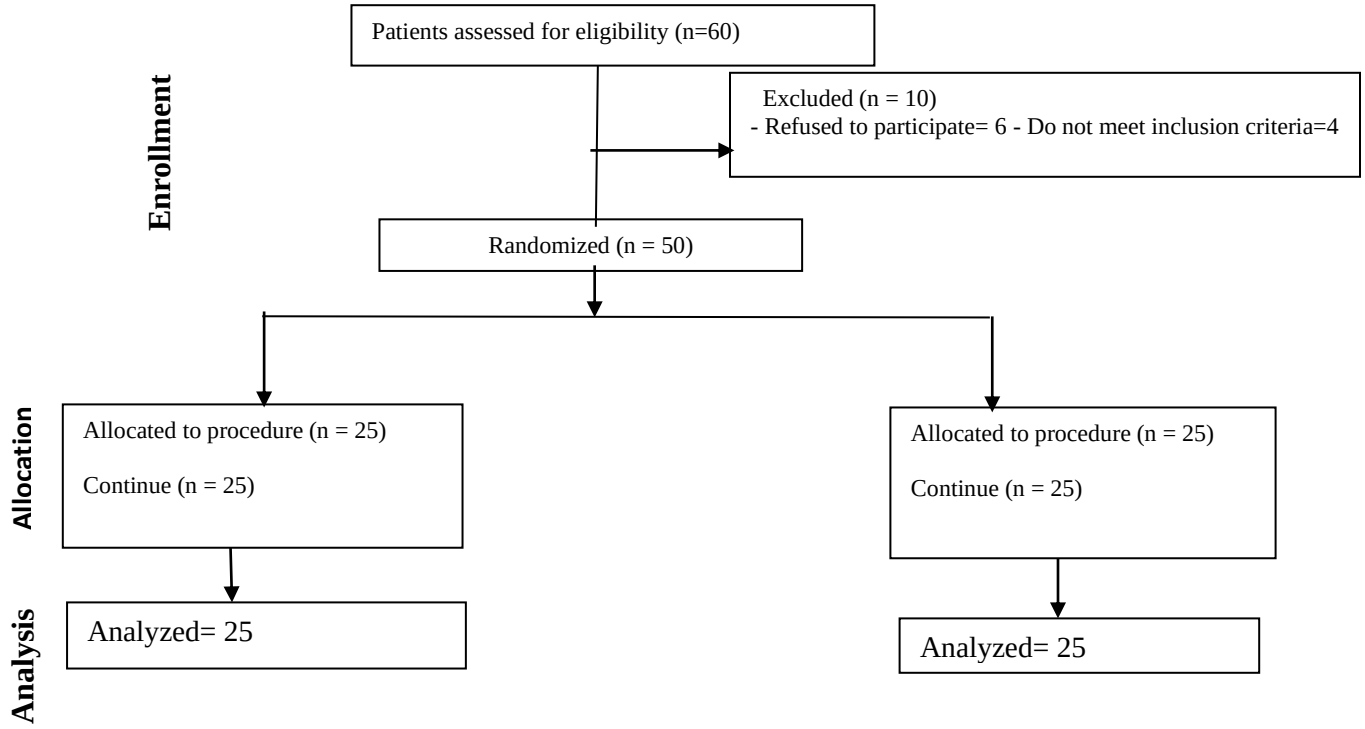

Figure (1): Flow chart

Preoperative assessment and preparation:
A careful medical history was taken, a general examination, vital signs were assessed and routine laboratory investigations were done.

Anxiety and patient satisfaction score:
Preoperative anxiety was assessed before induction of anesthesia according to a seven-point scale (1 = relaxed, 2 = apprehension, 3 = mild anxiety, 4 = moderate anxiety, 5 = manifest anxiety, 6 = severe anxiety, 7 = very severe anxiety) [9]

Patient satisfaction score: at the end of 24 hours postoperative a 5-point scale; 0 = poor, 1 = fair average, 2 = moderate, 3 = good, and 4 = excellent [9]

Visual analoge scale (VAS):
The pain severity was assessed immediately after recovery from anesthesia and then in the 2, 4, 6, 8, 12, and 24 hours after surgery. Patients were asked to make a horizontal mark across the line at the place that indicated the amount of their pain sensation, when it was more or equal to 3 cm we gave analgesia using fentanyl by a dose of 1 Microgram per Kg [10]

The study technique:
On the patient's arrival to the operating room, a 20 G intravenous cannula was inserted in a peripheral vein at the dorsum of the hand and ringer lactate infusion started at 5-10ml\kg\hour., standard monitoring commenced such as noninvasive blood pressure (NIBP), Electrocardiography (ECG), Oxygen saturation by a pulse oximeter, and Bispectral index (BIS) value monitoring (Silver pre-gelled electrodes (Aspect Medical Systems, Natick, MA, USA) were applied to the left and right frontal regions and referred to a vertex electrode (C2) which computed the BIS) [11]. BIS value was generated every 10 seconds to obtain baseline data before induction of anesthesia.

Induction and maintenance of balanced anesthesia:
Preoxygenation was done by asking a patient to take 4 deep breaths using an oxygen mask 10L\min. Induction of anesthesia was done for all patients with Fentanyl (2-5µg/kg), Propofol (2 mg/kg), and atracurium (0,5mg/kg) then followed by insertion of the endotracheal tube by using a laryngoscope. Maintenance of anesthesia was done by isoflurane, oxygen 5 liter, and atracurium (0,1 mg/kg intermittent every 20-30 minutes). Titration of isoflurane was guided by bispectral index (BIS=40–50) and hemodynamic endpoints (mean arterial pressure from 70:80 and heart rate less than 80).

Patients were adequately positioned and ventilated using volume-controlled mode (tidal volume of 8 ml/kg, respiratory rate (RR) 12, and PEEP 5) then the patient was carefully turned prone with proper padding of both eyes with soft pads under pressure sites, both arms are never extended more than 90 (to avoid a stretch of the brachial plexus), and careful position of both legs (to avoid overstretching sciatic and common peroneal nerve).

Carefully check chest inflation to confirm proper ventilation till the end of the operation. All patients were receiving paracetamol infusion 1gm intravenous (I.V) over 10 min after starting of skin incision. Because isoflurane titrated using BIS alone might provide hypnosis but insufficient analgesia, So, the protocol allowed to increase the inspired isoflurane concentration if BIS exceeded 5 (a maximum allowable increase of isoflurane was 2% for 5 min), if this did not achieve the targeted values of blood pressure and heart rate, analgesia in the form of 0.5–1 microgram/kg boluses of fentanyl were used as required.

After the end of the operation, patients turned supine and neuromuscular blockade was reversed (with I.V atropine 0.02mg / Kg and neostigmine 0.04 mg/kg), after the return of spontaneous respiration. All the patients were extubated on the table when awake and following commands. Patients were closely monitored 24hours after surgery in the neurosurgical department for follow-up and to detect postoperative analgesic requirement (When VAS was more or equal to 3cm we gave analgesia using fentanyl by a dose of 1 Microgram per Kg) and the occurrence of any complication.

Statistical analysis:
Collected data were analyzed using the statistical software SPSS, Ver.22. (SPSS Inc, Chicago, IL, USA). Descriptive statistics, Chi-square test, and t-test were performed to analyze the results. The $p<0.05$ was considered significant.

Results

In the present study, 50 patients with a mean age of 46.68±9.59 years, of whom 28 were males and 22 were females, were included. Patients were randomly divided into two groups Group A; study group (n=25) and group B; placebo group (n= 25). Regarding the patients' characteristics, no differences were observed in the patient demographics and surgical profiles between both groups (Table 1).

The mean preoperative anxiety score was significantly lower in the study group compared with the control group (1.2±0.5) versus (3.8±1.7), respectively. Requirement for additional intraoperative analgesic use was determined in 52% of patients in the study group and 48% needed only one dose while the majority of the control group (96%) were given more than one dose of analgesic The time for the first request for postoperative analgesia showed statistically highly significant longer duration in the study group compared to control group, and the total dose of fentanyl required during the first 24 h post-operatively showed highly statistically significantly lower values in the study group compared to control group ($P < 0.0001$), (Table 3).

There was a significant difference between the study and control groups in terms of the level of patient satisfaction (p=<0.0001). In the study group 24%, 60%, and 12% of the patients, respectively, rated the treatment as excellent, good, or moderate. Nine patients in the control group (36%) and 44% of patients rated the treatment as "fairly well – poor" (Table 4).

We noted that VAS was significantly lower in the study group in comparison with the control group post-operative with a P value < 0 .001. Also, we noted an insignificant increase in VAS score at the 6th hr postoperative in both groups which return to a decrease at the 8th hr in the study group without any decrease in the control group (Table 5).

There were no significant differences between the groups in terms of the rates of postoperative nausea, vomiting, and dizziness (not shown in the tables).

Table (1): patient's characteristics data

	Group A (gabapentin + celecoxib) (n=25)	**Group B (Placebo) (n=25)**	**p-value**
Age (years)			
Mean±SD	45.7±8.2	49.5±9.7	0.1
(Range)	(32-60)	(30-60)	
Sex			
Males	14 (56%)	14 (56%)	0.9
Females	11 (44%)	11 (44%)	
Duration of surgery (min.)			
Mean±SD	115.6±25.5	110.2±12.8	0.3
(Range)	(80-160)	(80-120)	
Cause of operation			
Sensory loss	4 (16%)	4 (16%)	0.9
Motor deficit	10 (40%)	9 (36%)	
Failure of medical treatment	11 (44%)	12 (48%)	

Table 2: Pre-operative anxiety score and Intra-operative analgesic requirements

Variables	Group A (gabapentin + celecoxib) (n=25)	Group B (Placebo) (n=25)	p-value
Anxiety score Mean±SD	1.2±0.5	3.8±1.7	<0.0001
Intra-operative analgesic requirements			
No need for analgesics	13 (52%)	0 (0%)	<0.0001
One dose	12 (48%)	1 (4%)	
≥one dose	0 (0%)	24 (96%)	

Table 3: Post-operative analgesic (fentanyl) requirements

Variables	Group A (gabapentin + celecoxib) (n=25)	Group B (Placebo) (n=25)	p value
Time for first analgesic request (hrs) Mean±SD	5±1.8	1.2±0.4	<0.0001
Total dose of fentanyl over 24 h (microgram)	150±90	390±90	<0.0001

Table 4: Post-operative satisfaction score

satisfaction score	Group A (gabapentin + celecoxib) (n=25)	Group B (Placebo) (n=25)	p-value
Excellent	6 (24%)	0 (0%)	<0.0001
Good	15 (60%)	0 (0%)	
Moderate	3 (12%)	5 (20%)	
Fair	1 (4%)	9 (36%)	
Poor	0 (0%)	11 (44%)	

Table (5): Comparison of postoperative pain score (VAS)

VAS	Group A (gabapentin + celecoxib) (n=25)	Group B (Placebo) (n=25)	p value
Immediately after recovery	1 (0-2)	4 (2-4)	<0.001
2h	2 (1-2)	5 (5-6)	<0.001
4h	2 (2-2)	5 (5-6)	<0.001
6h	3 (2-4)	6 (5-7)	<0.001
8h	2 (2-3)	7 (5-7)	<0.001
10h	2 (1-2)	7 (5-7)	<0.001
12h	2 (2-2)	6 (6-7)	<0.001
24h	2 (2-2)	6 (5-6)	<0.001

Data presented as Median (IQR)

Discussion

In our study, using preemptive administration of gabapentin 300mg plus celecoxib 200mg 2hr preoperative in the patients undergoing complex spine surgery we found that it provided lower preoperative anxiety, perioperative analgesic requirement, postoperative VAS and led to high postoperative patient satisfaction score.

Complex spine surgery can be defined as thoracolumbar spine surgery with instrumentation, laminectomy at three or more levels, or scoliosis surgery to improve long-term pain and quality of life in symptomatic patients with back diseases associated with significant postoperative pain[12]. Inadequate treatment of post-operative pain can lead to patient dissatis-faction with the surgical experience and may have adverse psychological consequences; so, an essential part of perioperative care is postoperative pain management[13].

Recently, both preemptive analgesia and multimodal analgesia have been proposed with acceptance in addressing pain management [14]

In agreement with our results for preoperative anxiety and postoperative satisfaction scores, Vasigh et al., (2016)[6] (who used the same combination of preemptive gabapentin plus celecoxib in the same doses as us) found that the mean anxiety score in the gabapentin group was significantly lower compared to the placebo and gabapentin plus celecoxib group respectively ($p < 0.001$, $p<0.05$) without significant difference between gabapentin group and gabapentin plus celecoxib group and also found patient satisfaction was significantly higher in gabapentin plus celecoxib group compared to the placebo and gabapentin group ($p< 0.05$). So, there was no significant benefit for using a high dose of gabapentin (600

mg) in either lowering anxiety score or improving patient satisfaction.

Also, Mehran Soleimanha et al., (2018)[15] who compared the case patients (who were given preemptive multimodal analgesia celecoxib, acetaminophen, and gabapentin) with the control group, found a meaningful difference in the anxiety severity of both two groups ($p<0.0001$) in a way that the percentage of relatively severe and severe and very high anxiety in the group of combinative drugs was 39% has been less than the placebo group which was 62% and found that patient satisfaction was more in the combination group than placebo. In this study, the first morphine use time in the group of combinative drugs is more than the time in the placebo group, and regarding the dose of consumption, the group of the combinative group ($7/6 \pm 2/5$) is less than the placebo group ($46 \pm 7/9$).

Although some studies show that pretreatment with 600 mg of gabapentin decreases anxiety in lumbar surgery [16]. However, Clarke et al., (2010) [17] who tried a trial of multimodal analgesia by giving gabapentin 600 mg 2 hours before spinal anesthesia in total hip arthroplasty found that the median of their anxiety score increased in the placebo group but decreased in gabapentin group with no significantly different between the groups either before ($P = 0.95$) or two hours after ($P = 0.61$) ingestion of gabapentin or placebo but in our result, there was a significant decrease in anxiety score in the study group when compared with the control group this difference in result may be due to the difference of age group, number of patients, different type of operation and different type of anesthesia so that according to our study result it may be better to use a combination of gabapentin and celecoxib in low doses rather than using gabapentin alone in a higher dose.

According to Paul et al., 2013[18] results, found that preemptive gabapentin has no effect on patient satisfaction, but another randomized double-blind clinical trial found that patient satisfaction was significantly higher in the gabapentin group than those of the placebo and celecoxib groups ($P < 0.05$) but higher doses of gabapentin and celecoxib were needed to increase patient satisfaction[9]. In our study, we get sufficient satisfaction after using a combination of both drugs in lower doses than them.

Our study revealed that lower intraoperative analgesic requirement in the study group compared with the control group with a significant difference and p-value <0,001 and this was in agreement with Doha et al., (2010)[19] who found that by giving oral gabapentin 1200mg, two hrs. before surgery there was a significant reduction in the intraoperative fentanyl requirements after using gabapentin preoperatively.

Regarding VAS, it was significantly lower in our study group when compared with the control group immediately after recovery, post-operative (P value 0.001). By comparing our result with Pandey et al., (2004)[20], Patients in the gabapentin group had significantly lower VAS scores than those in the placebo group and the total fentanyl consumed after surgery in the first 24 h in the gabapentin group (233.5 ± 141.9) was significantly less than in the placebo group (359.6 ± 104.1; $P < 0.05$), these results were in agreement with our result in using gabapentin in the same dose like us as preemptive analgesia.

Vasigh, Najafi et al., (2016) [9] also found that VAS decreased more in gabapentin than celecoxib without a significant difference but with a significant difference in comparison to placebo and total morphine consumption in the placebo group, gabapentin and celecoxib was 30.1 ± 0.6, 11.9 ± 4.4 and 22.8 ± 6.8 respectively, so the means of morphine consumption in the gabapentin group were significantly lower than those of the celecoxib and placebo groups respectively ($P < 0.001$, $P < 0.05$). In our result, we found the same effects in the study group

by using a combination of both drugs in lower doses than they used.

Also, Mahjoubifard et al., (2016)[21] results detected the superiority of celecoxib in pain control at least for two hours in addition to the total painless period after surgery and perfectly decrease postoperative opioid consumption, the participants in the control group got half case patients' opioids (P= 0.047) in agreement with our results (P< 0.0001) in using celecoxib in the same dose as preemptive analgesia.

Waraporn, et al., (2011)[22] found that a combination of celecoxib and gabapentin together had lower postoperative analgesic requirements than celecoxib and gabapentin alone but without change in pain score and other side effects of the medications.

Although a systematic review and meta-analysis. a study by Yu Lin et al., demonstrated that both preoperative gabapentin and pregabalin significantly reduced postoperative pain and narcotic consumption after lumbar spinal surgery when compared with placebo,[23], recently Kang et al., in another meta-analysis study found that gabapentin alone did not decrease postoperative pain, cumulative morphine consumption and the incidence of adverse effects after total knee and hip arthroplasty and didn't find enough evidence to support the administrations of gabapentin for postoperative pain[24]

Conclusion

The study showed that a combination of gabapentin plus celecoxib had an additive effect compared to the use of each drug alone. So using this combination of gabapentin 300mg plus celecoxib 200mg 2hr preoperative as preemptive multimodal analgesia in the patients undergoing complex spine surgery provided lower preoperative anxiety, VAS, perioperative analgesic requirement and led to high postoperative patient satisfaction score.

Limitations:

limitations of our study, first it was part of a single center with a relatively small sample size including patients who were ASA I and II and underwent elective complex spine surgery with subjective anxiety, satisfaction, and perception of pain by patients (self-answer questionnaire). Therefore, study results cannot be generalized to the general population. Second, preoperative side effects were not followed up in patients receiving the combination of gabapentin and celecoxib. However, there were no severe preoperative side effects enough to lead to exclusion from the study. Finally, there was no pharmacokinetics and pharmaco-dynamics evaluation of the combination treatment effect.

Recommendations:

We recommend further multicenter studies: to test different doses of used drugs, on a large number of patients, in different types of surgery, with a good assessment of chronic post-surgical pain (CPSP) by prolonged time for follow-up. Also, we recommend a cost-effectiveness study of the combination for a more accurate evaluation.

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