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Safety and Efficacy of Prgabalin as a Part of Multimodal Analgesia in Patients with Lumbar Spine Disk Surgery

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Abstract

Background: *Inadequate pain control after lumbar disc herniation surgeries may increase morbidity; leading to prolonged hospital stays, and increase medical costs. The anti-epileptic drugs such as pregabalin with non-steroidal anti-inflammatory drugs (NSAID) were used as a part of multimodal analgesia to control such pain.*

Aim of the study: *The aim of this randomized double-blinded study was to assess the safety and efficacy of using pregabalin as a part of multi modal analgesia on pain relief in patients underwent posterior approach lumbar spine disc surgery.*

Methods: *A prospective, comparative blinded randomized study was carried out on one hundred patients of both gender, ASA I and II, aged between 21-60 years old scheduled to undergo elective posterior approach lumbar spine disc surgery. Patients were randomly assigned into two groups (50 patients each);* ***Group (p)*** *received Pregabalin 150 mg capsule 2 hours preoperative and the same dose 6 hours postoperative and* ***Group (C)*** *received Placebo capsule 2 hours preoperative and the same dose 6 hours postoperative. Intra operative hemodynamics and post operative following parameters were recorded; mean arterial pressure, heart rate, respiratory rate, Visual Analogue score and Patient satisfaction score: at the end of postoperative period.*

Results: *No significant difference was found in demographic data between both groups. Pregabalin administration associated with a better control of intra and post operative mean arterial pressure and heart rate P values were (p<0.016) (p<0.018) respectively when compared to placebo. Regarding VAS scores in both groups there was decrease but more significant in Group (P) especially in first 8 hours (p<0.001). The same as satisfaction score.*

Conclusion: *We concluded that Pregabalin provides pain relief and good hemodynamic control when administered 2 hours per operatively and patient's satisfaction was very good after elective lumbar disk surgeries. .*

Keywords: *Pregabalin - celecoxib - spine disk surgeries - VAS score.*

1. Introduction and Aim of the Work

Pregabalin was synthesized in 1991 and approved for the treatment of neuropathic pain and refractory epilepsy in 2004 and It is one of two available a 2-d ligands, pregabalin and gabapentin, known as the gabapentinoids. Pregabalin and gabapentin share a similar mechanism of action with the difference related to pharmacokinetic and pharmacodynamic characteristics, and pregabalin has a faster onset time and a more predictable absorption profile than gabapentin. [1-2]

Surgical and conservative treatments had long-term beneficial effects on sciatica symptoms in patients with lumbar disc herniation. Compared with conservative treatment, surgical treatment relieved back pain faster, but no relevant clinical difference was observed after 3 months. Surgical treatment may thus be attractive to patients with debilitating pain symptoms who seek quick relief, or who did not experience satisfactory improvement with conservative treatment. [3-4]

Spine surgery may be recommended if non-surgical treatment such as medications and physical therapy fails to relieve symptoms. Surgery is only considered in cases where the exact source of pain can be determined such as a herniated disc, scoliosis, or spinal stenosis. [5]

The presence of high-quality analgesia in the postoperative period is very important, to relieve post-surgical pain and improve well-being, and also because inadequate pain control may increase morbidity, lead to prolonged hospital stays, and increase medical costs. [6]

While opioids provide effective analgesia, their use can be limited by side effects in the perioperative period. [7]

The Anticonvulsants drugs such as Pregabalin when used with non-steroidal anti-inflammatory drugs (NSAID) as a part of multimodal analgesia provide good control of such pain. Pregabalin is an anticonvulsant drug that has analgesic effect in post-herpetic neuralgia, diabetic neuropathy, and neuropathic pain. [8]

The aim of this randomized double-blinded study was to assess the safety and efficacy of using pregabalin as a part of multi modal analgesia on pain relief in patients underwent posterior approach lumbar spine disc surgery.

2. Patients and Methods

After obtaining the local ethics committee of Minia University Hospital approval and written informed consent was taken from the patient, one hundred patients of both gender, American society of anesthesiologists (ASA) I and II, aged between 21-60 years old scheduled to undergo elective posterior approach lumbar spine disc surgery done by the same surgeon under general anesthesia, were enrolled in this prospective, randomized, double blinded controlled study.

Patients with a known sensitivity to pregabalin, psychotic disorder or cognitive impairment, history of drug dependency or substance addiction, history of chronic medical disease, the presence of coagulation disorders or pregnancy, were excluded from the study.

Preoperative data were collected two days before surgery as; demographic data, medical, surgical history, physical examination and routine laboratory investigations. The day before surgery, all patients were taught how to evaluate their own pain intensity using the Numerical Rating Scale (NRS), scored from 0-10 (where 0= no pain and 10=worst pain imaginable).

All patients were premedicated with midazolam 0.05 mg/kg and ranitidine 50 mg. After transferring the patients to the operative room; Peripheral Venous line was established and an infusion of lactated ringers' solution was started and basic ASA monitors were attached.

Surgery was performed under standard general anesthesia for all patients and postoperative analgesia was provided through patient controlled Intravenous - analgesia (PCIA) using morphine for 24 hours.

Patients were randomly assigned into two groups (50 patients each) by using opaque sealed envelopes containing computer generated randomization schedule, the opaque sealed envelopes were sequentially numbered that were opened before application of anesthetic plan.

- **Group (P)** received Pregabalin 150 mg capsule 2 hours preoperative and the same dose 6 hours postoperative.
- **Group (C)** received Placebo capsule 2 hours preoperative and the same dose 6 hours postoperative.

General anesthesia was conducted for patients of both groups by three minutes pre-oxygenation, intravenous induction was done by propofol (1.5 mg/kg) and fentanyl 2 µg/kg administered over one minute. Tracheal intubation was performed after adequate neuromuscular blockade with cisatracurium 0.5 mg/kg. Anesthesia was maintained by sevooflurane 1-1.5 MAC, cisatracurium 0.03 mg/kg given when indicated. Patients were mechanically ventilated to maintain ETCO2 between 35-40 mmHg. The inspired oxygen fraction (FIO2) was 0.5 using oxygen-and-air mixtures then patient positioning was done and surgery was started. Carefully check about patient's position and chest infilation to confirm proper ventilation till the end of operation. All patients were receive antibiotic 2 gm and Ketorlac 15 mg plus paracetamol infusion 1gm intravenous (I.V) over 10 min before starting of skin incision.

At the end of surgery all patients turned supine and neuromuscular block was reversed in all patients with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and trachea was extubated in the operating room. Tracheal extubation was performed when patients met the following criteria: hemodynamic stability, adequate muscle strength, full consciousness, and

adequate ventilation breathing rate: 10 to 30 breaths/min, PaO2 /IFO2 ≥80/0.4, PaCO2, 30 to 45 mmHg). Intra operative rescue analgesic dose to all patients of both groups by fentanyl 1 μg g/kg intra operatively to maintain heart rate (HR) and blood pressure within 20% of the basal value.

All the patients were extubated on table when awake and following commands. Then patients closely monitored 24 hours after surgery in neurosurgical department and another two unknown capsules were taken 6 hours after operation according to the drug grouping. Intra operative assessment of hemodynamics: mean arterial pressure and heart rate before induction of anesthesia as a base line, after induction, after intubation within 5 min and every 5 minute intra operatively till the end of the operation.

Post operative assessment of patients was done for the following parameters: Hemodynamics as; mean arterial pressure and heart rate recorded 15 min, 30 min, one hour then every two hour till 24 hours postoperative.

Visual Analogue score: during 24 hours postoperative (a 10-point scale; 0 = no pain, 10= worst pain ever).

Patient satisfaction score: at the end of 24 hour postoperative a 5-point scale; 0 = poor, 1 = fair average, 2 = moderate, 3 = good and 4 = excellent (8).

2.1. Statistical Analysis

The required sample size was calculated using post hoc power analysis with accuracy mode calculations with MAP as the primary objective and therefore, it was estimated that minimum sample size of 49 patients in each study group would a chive a power of 80% to detect an effect size of 0.8 in the outcome measures of interest, assuming a type I error of 0.05 All analyses were performed with the SPSS 22.0 ® software. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD). And Mann–Whitney test were used to compare between two groups while Chi square test was used for qualitative data. Where compare between continuous variables by t-test. P was considered significant if <.05 at confidence interval 95%.

3. Results

Table1: *patient's demographic data (Data are presented as range, mean ± SD).*

	P((N=50))	C(N=50)	p value
Age (yrs) Mean±SD(Range)	44.7±9.7(30-60)	42.4±10.9(21-61)	0.077
Sex			0.929
Male	30 (60%)	32 (64%)	
Female	20 (40%)	18 (36%)	
Duration of surgery (min.) Mean±SD(Range)	115.6±26.6 (80-160)	112.4±15.9(90-140)	0.129
Cause of operation			0.923
• Sensory affection	14 (28%)	10 (20%)	
• Motor affection	18 (36%)	16 (32%)	
• Failure of medical treatment	18 (36%)	24 (48%)	

One way ANOVA test for parametric quantitative data between the four groups, Chi square test for qualitative data Significant difference at p value < 0.05.*

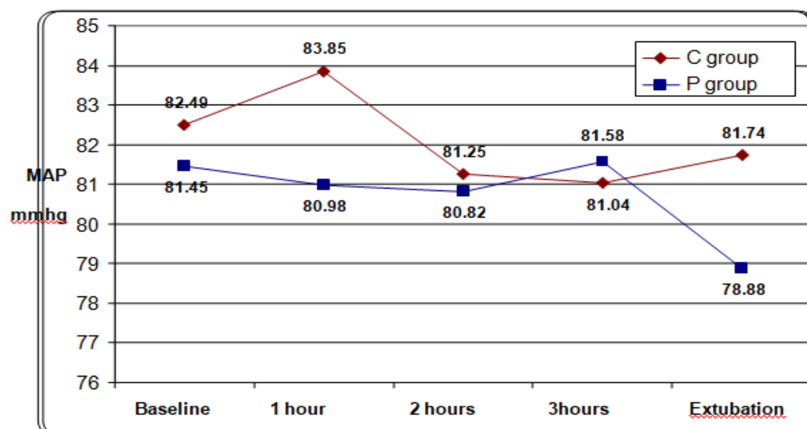

Figure1: *Intra operative MAP*

- *One way ANOVA test for parametric quantitative data between the two groups 2 groups*
- ** Significant difference between groups at p value < 0.05*

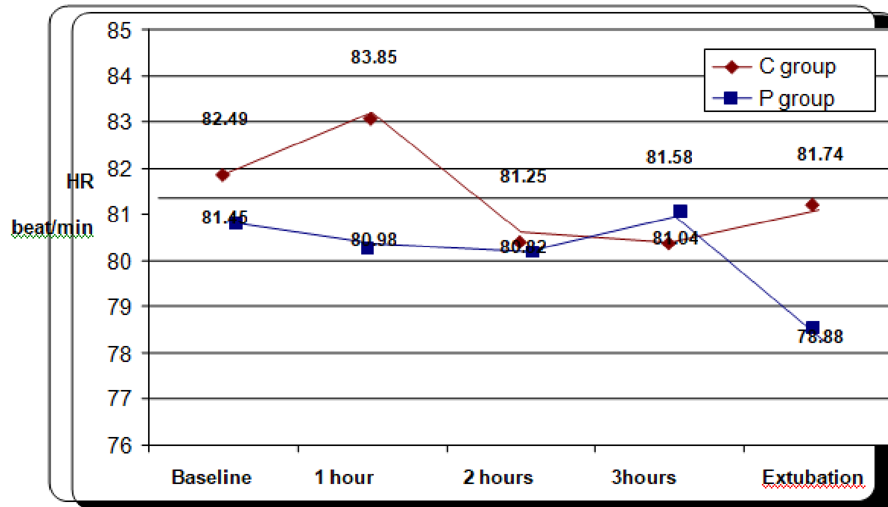

Figure2: *patient's Heart rate intra-oper*

- *One way ANOVA test for parametric quantitative data between the two groups 2 groups*
- ** Significant difference between groups at p value < 0.05*

Table2: *Comparison of Postoperative hemodynamics (Data presented in mean ± SD)*

	P(n=50	C(n=50)	p value
	Mean±SD	*Mean±SD*	
30 min			
HR (beat/min)	85.7±7.3	88.0±10.7	**<0.001***
MAP (mmHg)	73.4±16.6	78.0±6.7	**<0.001***
1h			
HR (beat/min)	85.4±6.8	89.5±9.8	**<0.001***
MAP (mmHg)	76.2±9.8	78.2±8.6	**<0.001***
2h			
HR (beat/min)	87.2±8.7	89.3±9.9	**<0.001***
MAP (mmHg)	71.5±18.7	75.0±6.7	**<0.001***
4h			
HR (beat/min)	86.2±9.2	90.6±8.7	**<0.001***
MAP (mmHg)	77.0±6.7	79.5±18.7	**0.001***
6h			
HR (beat/min)	80.3±11.6	86.8±14.3	**<0.001***
MAP (mmHg)	77.5±18.7	81.0±6.7	**<0.001***
8h			
HR (beat/min)	86.4±6.9	89.2±12.2	**<0.001***
MAP (mmHg)	72.5±18.7	76.0±6.7	**<0.001***
10h			
HR (beat/min)	84.2±6.1	87.0±11.3	**<0.001***
MAP (mmHg)	72.5±18.7	74.4±6.9	**<0.001***
12h			
HR (beat/min)	82.6±6.6	86.1±13.8	**<0.001***
MAP (mmHg)	73.5±18.7	77.0±6.7	**0.002***
18			
HR (beat/min)	84.2±11.5	85.5±9.8	**<0.001***
MAP (mmHg)	71.5±18.7	75.0±6.7	**<0.001***
24h			
HR (beat/min)	83.5±14.2	88.0±9.7	**<0.001***
MAP (mmHg)	79±8.6	81.2±7.3	**0.015***

- *One way ANOVA test for parametric quantitative data between the two groups*
- *Significant difference between groups at p value < 0.05.*

Table3: *Post-operative VAS*

Post-operative VAS	Group C (n=50)		Group G (n=50)		P. value
	Range	Mean±SD	Range	Mean±SD	
VAS 0 h	1 - 4	2.6 ± 1	1 - 2	2.1 ± 0.9	0.049*
VAS 4 h	1 - 3	2.4 ± 0.9	1 - 2	2.0 ± 0.5	0.006*
VAS 8 h	1 - 3	2.3 ± 0.5	1 - 2	2.1 ± 0.5	0.012*
VAS 12 h	2 - 3	3 ± 0.8	1 - 3	2.4 ± 0.8	0.006*
VAS 16 h	2 - 4	3.1 ± 0.8	1 - 3	2.7 ± 1.1	0.177
VAS 20 h	1 - 4	2.5 ± 0.9	1 - 3	2.3 ± 0.7	0.527
VAS 24 h	1 - 4	3.2 + 1	2 - 3	2.7 + 0.9	0.058

Figure3: *comparison of postoperative satisfaction score. (Data presented in number and percentage).*

Table4: *Comparison of analgesic among studied groups,*

Mean/ SD	Group P No=50	Group C (N=50)	P-Value
Time of 1st dose request	5.13 ± 1.008	3.27 ± 0.9	<0.001**
Total analgesic consumption mg/ 24 hours	6.27± 0.8	12.18+0.74	<0.001**

Data *expressed as (Mean ± SD)*

P. value < 0.05 *considered statistically significant.*

4. Discussion

Although pregabalin is frequently used for treatment of various chronic pain states, evidence of a beneficial effect is inconclusive, and the incidence of adverse events may be increased. The first trial on pregabalin for acute pain treatment was published in 2001, and since then the literature has continued to suggest a beneficial effect of pregabalin in acute postoperative pain management. Furthermore, an increasing number of systematic reviews with meta-analyses have been published suggesting that pregabalin has both opioid-sparing and pain reducing effects. [9-11]

The goal of a lumbar disk surgery is usually to relieve pain caused by nerve root pinching symptoms usually consist of back and leg pain with sensory and motor deficits in the lower legs that worsen by walking longer distances. Symptoms are classically relieved by lumbar flexion. Failure of conservative treatment is an indication for surgery. The goal of surgery is to decompress the spinal canal and dural sac from degenerative bony and ligamentous overgrowth. [12-13]

Multimodal analgesic arose to allow synergistic effects of different analgesics used at a lower dose to reduce side effects and limit the amount of opioids consumed and provide more effective postoperative pain control than opioids alone. Component therapies of multimodal analgesia with substantial evidence to support efficacy in postoperative patients include gabapentinoids, acetaminophen, ketamine, non-steroidal anti-inflammatory drugs and regional anesthesia. [14-15]

In the subgroup analyses exploring the effect of a single dose of pregabalin on 24 h morphine

consumption, many trials with overall low risk of bias found a reduction of 10.1 mg on 399 participants post operative. [16-17]

According to hemodynamics in peri-operative period in our study we found that HR and MAP were significantly lower in the three groups (G) when compared with group C. Mahjoubifard, et al., 2016, Studied 99 patients underwent major orthopedic surgery. They were randomly allocated into four groups. One to two hours before anesthesia, they received midazolam 7.5 mg plus study drugs. Group P received placebo plus placebo at 12 and 24 hours later. Group C received celecoxib 400 mg plus celecoxib 200 mg at 12 and 24 hour later. Group P received gabapentin 300 mg at 12 and 24 hour later. Finally, group CG received celecoxib 400 mg + gabapentin 400 mg plus celecoxib 200 mg + gabapentin 300 mg at 12 and 24 hour later, This study found that there was no difference regarding hemodynamics in post-operative period (systolic blood pressure, diastolic blood pressure and respiratory rate) between the four groups at any time that may be owing to the different in procedures done in this study. [18]

By comparing our result with (Pandey et al., 2004) who studied fifty-six ASA I and II patients were randomly allocated into two equal groups to receive either gabapentin 300 mg or placebo two hours before lumbar discoidectomy surgery. After surgery, the pain was assessed on a visual analogue scale (VAS) at intervals of 0–6, 6–12, 12–18, and 18–24 hr at rest, Patients in the gabapentin group had significantly lower VAS scores gradually at all-time intervals than those in the placebo group at the first 6hr post-operative the mean pain score was 3.5 ± 2.3 in gabapentin group and 6.1 ± 1.7 in placebo group and our result found at the 1st 6 hr the median pain score in the three groups (GC, G, C) was 3 and in placebo was 6, so that at the 1st 6 hr postoperatively this result was in agreement with our result in using gabapentin in the same dose but we use it with combination of celecoxib as preoperative preemetive multimodal analgesia for post-operative pain management. [19]

In another study the pain score continue to decrease in Pregabalin group in the all-time intervals that didn't happen in our study and we found that there was insignificant increase in VAS score at the 6th hr postoperative and decreasing of VAS score started at the 8th hr in group GC ,at the 10th hr at group G then in the 24th hr in group C , this different in the effect after 6 hr post-operative may be related to our post-operative analgesic dose and different of type of surgery . [20]

And (Waraporn et al., 2011) recorded pain score at 1, 4, 8, 12, 16, 20, and 24 hours postoperatively using numerical rating scale (NRS) which decrease in group GC , C and G respectively but with no significant difference between the four groups at all-time interval except hour 24 (p-value 0.014) and Comparing group by group at hour 24, no significant difference was found this study disagree with our study , this dis agreement may be related to different types of operation which were included in their study. [21]

During studying we noted that patient satisfaction score was significantly higher in the group (G) respectively when compared with group C with P value < 0.001, which agree with *(Vasigh, Jaafarpour, et al., 2016)*who found that the Pregabaline plus NSAID group patient satisfaction was significantly higher compare to the placebo and Pregabaline group (p< 0.05). [22]

We compare our result with ***(Bhartiet al ., 2013)*** who used preoperative gabapentiods in mastectomy operation and studied 40 patients divided into two groups, gabapentiods group received gabapentiods 300 mg orally 1 hour preoperative and the control group received placebo , Patients in the gabapentiods group showed lower intra operative heart rate and mean arterial pressure at base line , after induction, after intubation , 5 min post intubation (as suppression hemodynamic response to stress of intubation) and none of the patients had bradycardia or need vasopressor , which was in agreement with our result by using the combination of gabapentiods and celecoxib in lower dose than they did. [23]

We also continuous monitoring of hemodynamic all over the time of operation and we found that intra operative hemodynamics (HR and MAP) were significantly lower in the group (P) compared with group C (p value <0,001) against the study by who didn't find any hemodynamic values change in all intra operative times. [24]

We concluded that both Pregabalin plus NSAID provide pain relief and good hemodynamic control when administered perioperatively and much better patient's satisfaction after elective lumber disk spine surgeries. .

In our study there were some limitations as: Some of our study parameters were subjective, emergency spine fixation surgeries were excluded which associated with head trauma with deterioration of Glasgow coma scale (GCS) and finally enough studies used the same combination of our study drugs and no enough studies measured the same parameters that we measured in our study.

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