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Safety of gabapentin versus celecoxib as a part of multimodal analgesia in patients with elective spine fixation surgery, A comparative randomized control study

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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 gabapentin and other non-steroidal anti-inflammatory drugs (NSAID) such as celecoxib 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 asses and compare the efficacy of using gabapentin versus celecoxib as a part of multi modal analgesia in perioperative hemodynamic control and 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 (G) received gabapentin 300 mg capsule 2 hours preoperative and the same dose 6 hours postoperative and Group (C) received celecoxib 200 mg 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. Gabapentin 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 celecoxib. Regarding VAS scores in both groups there was decrease but more significant in Group (G) especially in first 8 hours ($p<0.001$). the same as satisfaction score.
Conclusion: We concluded that both Gabapentin and celecoxib provide pain relief and good hemodynamic control when administered perioperatively but Gabapentin provide much better patient's satisfaction after elective spine fixation surgeries.

Keywords: Gabapentin - celecoxib - spine fixation surgeries - VAS score

Introduction and aim of the work
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 [1, 2].
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 [3].
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 [4].
While opioids provide effective analgesia, their use can be limited by side effects in the perioperative period [5].
The anti-epileptic drugs such as gabapentin and other non-steroidal anti-inflammatory drugs (NSAID) such as celecoxib were used as a part of multimodal analgesia to control such pain. Gabapentin is an anticonvulsant drug that has analgesic effect in post-herpetic neuralgia, diabetic neuropathy, and neuropathic pain. Celecoxib is one of the NSAIDs, that its analgesic effect is reported in various studies by cyclooxygenase-2 (COX-2) inhibitor [6, 7].
The aim of this randomized double-blinded study was to asses and compare the efficacy of using gabapentin versus celecoxib as a part of multi modal analgesia in perioperative hemodynamic control and pain relief in patients underwent posterior approach lumbar spine disc fixation surgery.

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 fixation 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 celecoxib or 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 Visual Analog Scale (VAS) [8], 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 fentanyl for 48 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 (G) received gabapentin 300 mg capsule 2 hours preoperative and the same dose 6 hours postoperative.

-Group (C) received celecoxib 200 mg 2 hours preoperative and the same dose 6 hours postoperative.

General anesthesia was conducted for patients of both groups as following

After 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 isoflurane 1-1.5 MAC, cisatracurium 0.03 mg/kg given when indicated. Patients were mechanically ventilated to maintain $ETCO_2$ between 35-40 mmHg. The inspired oxygen fraction (FIO_2) 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 paracetamol infusion 1gm intravenous (I.V) over 10 min after 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, PaO_2 /IFO_2 ≥80/0.4, $PaCO_2$, 30 to 45 mmHg).

Intra operative analgesia in both groups by continuous intravenous fentanyl infusion 1 µg g/kg/hr intra operatively to maintain heart rate (HR) and blood pressure within 20% of the basal value. Fentanyl infusion was continued until end of surgery. 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, heart rate and oxygen saturation 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 (primary outcome).

Post-operative assessment of patients was done for the following parameters; (secondary outcomes).

- Hemodynamics as; mean arterial pressure, heart rate, and respiratory rate recorded 15 min, 30 min, one hour then every two hour till 24 hours postoperative.
- Visual Analogue score: during 48 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).

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%.

Results

Table 1: patient's characteristics data (Data are presented as range, mean ± SD).

	G (n=50)	C (n=50)	p value
Age (yrs)			0.077
Mean±SD	44.7±9.7	42.4±10.9	
(Range)	(30-60)	(21-61)	
Sex			0.929

Male	30 (60%)	32 (64%)	
Female	20 (40%)	18 (36%)	
Duration of surgery (min.)			
Mean±SD	115.6±26.6	112.4±15.9	0.129
(Range)	(80-160)	(90-140)	
Cause of operation			
• Sensory loss	14 (28%)	10 (20%)	0.923
• Motor deficit	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.

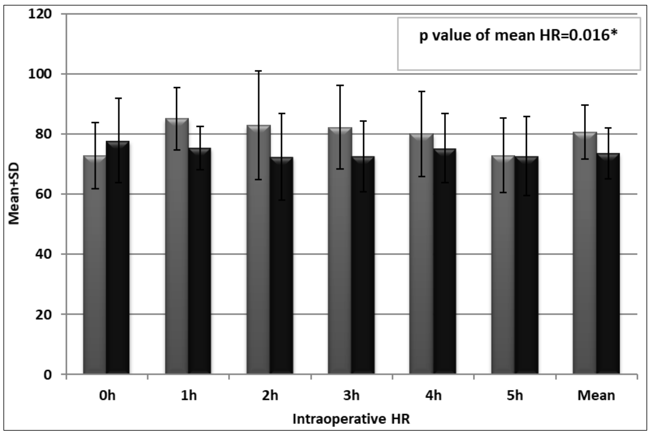

Fig 1: Intra operative heart ate (HR) [black column =group G and grey column = group C]

- One-way ANOVA test for parametric quantitative data between the two groups 2 groups

-* Significant difference between groups at p value < 0.05

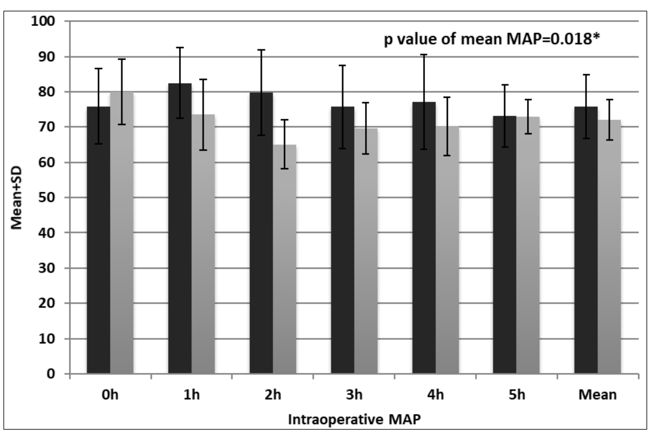

Fig 2: patient's Intra operative Mean Arterial Pressure [black column =group G and grey column = group C]

- One-way ANOVA test for parametric quantitative data between the two groups 2 groups

-* Significant difference between groups at p value < 0.05

Table 2: Comparison of Postoperative hemodynamics (Data presented in mean ± SD)

	G (n=50)	**C (n=50)**	**p value**
	Mean±SD	*Mean±SD*	
15 min			
HR (beat/min)	86.5±4.9	87.6±9.6	0.003*
MAP (mmHg)	78.5±18.7	82.0±6.7	<0.001*
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*
16h			
HR (beat/min)	84.5±11.7	88.4±11.7	<0.001*
MAP (mmHg)	74.5±18.7	78.0±6.7	0.004*
20h			
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.

Table 3: comparison of postoperative RR. (Data presented in mean ± SD.)

	G group	**C group**	**p value**
	Mean±SD	**Mean±SD**	
Before induction	14.3±2.6	13.2±2.5	<0.84

15 min	12.1±3.3	15.4±3.9	0.044
30 min	11 ±2.2	14.2±4	<0.002*
1h	11.7±2.2	14.9±3.8	<0.002*
2h	12.9±3.1	16 ±3.3	<0.001*
4h	12.1±3.6	16.4±3.8	<0.001*
6h	12±3.2	20±2.7	<0.001*
8h	13.8±3.4	15.4±1.9	<0.001*
10h	14.5±2.3	16.5±3.3	<0.001*
12h	18.3±2.6	18.4±3	<0.001*
16h	17.5±2.1	18.2±3.9	<0.001*
20h	14.8±2.1	18.5±3.6	<0.0136
24h	15.6±2.9	16.6±3.1	<0. 44

- One-way ANOVA test for parametric quantitative data between the two groups.
- * Significant difference between groups at p value < 0.05
- # means that control group was significantly different from other groups (p < 0.05).
- RR = respiratory rate

Table 4: 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
VAS 28 h	2 - 4	3.1 ± 0.8	1 - 3	2.7 ± 1.1	0.177
VAS 32 h	1 - 4	2.5 ± 0.9	1 - 3	2.3 ± 0.7	0.527
VAS 36 h	1 - 3	2.4 ± 0.6	1 - 3	2.6 ± 0.9	0.319
VAS 40 h	1 - 3	2.3 ± 0.7	1 - 3	2.1 ± 0.9	0.383
VAS 44 h	1 - 3	2.5 ± 1	1 - 2	2 ± 0.9	0.059
VAS 48 h	1 - 3	2.4 ± 1.2	1 - 2	2.5 ± 0.7	0.798

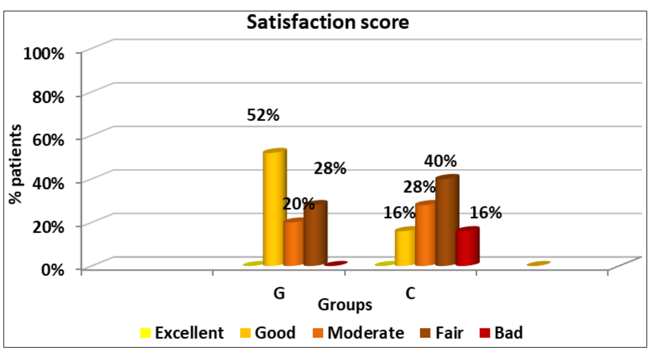

Fig 3: comparison of postoperative satisfaction score. (Data presented in number and percentage).

Discussion

The goal of a decompression 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. (9-10)

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.

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 G received gabapentin 400 mg plus 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 [11].

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 [12].

In another study the pain score continue to decrease in gabapentin 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 [13].

In (Waraporn et al., 2011) pain score recorded 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 [14].

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 gabapentin plus celecoxib group patient satisfaction was significantly higher compare to the placebo and gabapentin group (p< 0.05) [15].

We compare our result with (Bharti *et al*., 2013) who used preoperative gabapentin in mastectomy operation and studied 40 patients divided into two groups, gabapentin group received gabapentin 600 mg orally 1 hour preoperative and the control group received placebo, Patients in the gabapentin 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 gabapentin and celecoxib in lower dose than they did [16].

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 three groups (G) 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 [17].

We concluded that both Gabapentin and celecoxib provide pain relief and good hemodynamic control when administered perioperatively but Gabapentin provide much better patient's satisfaction after elective spine fixation surgeries.

In our study we faced 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.

References

1. Boenigks K, Echevarria GC, Nisimov E, Von Bergen Granell, AE, Cuff GE, Wang J, et al. Atchabahian A. Low-dose ketamine infusion reduces postoperative hydromorphone requirements in opioid-tolerant patients following spinal fusion: A randomised controlled trial. European Journal of Anaesthesiology (EJA). 2019; 36(1):8-15.
2. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. The Lancet. 2017; 390(10090):e21-e33.
3. Boktor J, Ninan T, Pockett R, Collins I, Sultan A, Koptan W. Lumbar fusion for lytic spondylolisthesis: Is an interbody cage necessary? Journal of Craniovertebral Junction and Spine. 2018; 9(2):101-106.
4. Ezhevskaya, Anna A, Mlyavykh Sergey G, Anderson D. Greg. 2013; 38(15):1324-1330.
5. Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RS, et al. Clinical aspects of acute post-operative pain management & its assessment. Journal of advanced pharmaceutical technology & research. 2010; 1(2):97-108.
6. Harsoor SS, Rani DD, Lathashree S, Nethra SS, Sudheesh K. Effect of intraoperative Dexmedetomidine infusion on Sevoflurane requirement and blood glucose levels during entropy-guided general anesthesia. Journal of anaesthesiology, clinical pharmacology. 2014; 30(1):25-30.
7. Kaya Refika, Orak Y, Balc lker. Comparison of the Effects of Intrathecal Fentanyl and Intrathecal Morphine on Pain in Elective Total Knee Replacement Surgery. Pain Research and Management, 2016, 5.
8. Chapman CR, Vierck CJ. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. The Journal of Pain. 2017; 18(4): 359.e351-359.e338.
9. Chen L, Mao J. Update on Neuropathic Pain Treatment: Ion Channel Blockers and Gabapentinoids. Curr Pain Headache Rep. 2013; 17(9):359.
10. Bordoni B, Marelli F. Failed back surgery syndrome: review and new hypotheses. Journal of pain research. 2016; 9:17-22.
11. Mahjoubifard M, Enayati H, Noori N, Mahdy S, Jahangiri Fard A. The Effect of Preemptive Oral Celecoxib on Pain Reduction and Opioid Consumption during Elective Herniorrhaphy. Enliven: J Anesthesiol Crit Care Med. 2016; 3(1):001.
12. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, Singh PK, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Canadian Journal of Anesthesia. 2004; 51(10):986-989.
13. Niu T, Lv C, Yi G, Tang H, Gong C, Niu S. Therapeutic Effect of Medical Ozone on Lumbar Disc Herniation. Medical science monitor: international medical journal of experimental and clinical research. 2018; 24:1962-1969.
14. Waraporn W, Theerawat C, Nuj T, Pet-eng S, Nadhaporn S. Combination of gabapentin and celecoxib for analgesia after major orthopedic surgery: a randomized, controlled trial. Asian Biomedicine. 2011; 5(1):101-110.
15. Vasigh A, Najafi F, Khajavikhan J, Jaafarpour M, Khani A. Comparing Gabapentin and Celecoxib in Pain Management and Complications After Laminectomy: A Randomized Double-Blind Clinical Trial. Iranian Red Crescent medical journal. 2016; 18(2):e34559-e34559.
16. Bharti N, Bala I, Narayan V, Singh G. Effect of gabapentin pretreatment on propofol consumption, hemodynamic variables, and postoperative pain relief in breast cancer surgery. Acta Anaesthesiologica Taiwanica. 2013; 51(1):10-13.
17. Mammoto T, Fujie K, Mamizuka N, Taguchi N, Hirano A, Yamazaki M, et al. Effects of postoperative administration of celecoxib on pain management in patients after total knee arthroplasty: study protocol for an open-label randomized

controlled trial. Trials. 2016; 17(1):45.