Research Article

Comparative evaluation of different doses of gabapentin and celecoxib as multimodal oral analgesia in patients of spine fixation surgery

Khaled A. Abdou, Al Shimaa I. Roushdy and Amna Th. Gadelrab Radwan
Department of Anesthesia, El-Minia Faculty of Medicine

Abstract

Introduction: Since an increased number of major spinal procedures, including revision surgery can be anticipated, we found it of relevance to assess a multimodal pain treatment strategy in patients undergoing surgery requiring instrumentation. **Aim of the work:** The aim of this randomized double-blinded study to asses and compare the efficacy of using different doses of gabapentin and celecoxib as combination for analgesia in postoperative pain relieve in patient underwent posterior approach lumbar spine 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, Patients were randomized to four groups (25 patients in each group): Group GC received gabapentin 300mg + celecoxib 200mg 2hr preoperative and the same combination 6 hr postoperative. Group G received gabapentin 300mg + celecoxib 200mg 2hr preoperative and gabapentin 300mg 6 hr postoperative. Group C received gabapentin 300mg + celecoxib 200mg at both 2hr preoperative and celecoxib 200mg 6 hr postoperative. Group O (placebo) as control group received empty capsules 2hr preoperative and 6 hr postoperative VAS score obtained from all patients immediately after recovery from anesthesia, at 2hr, 4hr, 6hr, 8hr, 10hr, 12hr and 24hr post-operative. **Results:** Postoperative VAS score was significantly lower in the three groups (GC, G and C) respectively when compared with group O. **Discussion:** Spinal procedures are associated with high level of postoperative pain compared to other surgical procedures and majority of patients report moderate to severe pain, which persists for at least initial 3-4 days. **Recommendation: Based on the current study we recommend:** Usage of preemitive multimodal analgesic with various mechanism of action is more useful in post-operative pain relieve after major surgery.

KeyWords: Acute neuropathic pain, Hour, Minimal invasive spine surgery, Noninvasive blood pressure.

Introduction

Acute postoperative pain remains to be a major problem, and inadequate or excessive treatment can cause side effect including increased risk of myocardial ischemia or infarction ,thrombo-embolic and pulmonary complications, persistent postoperative pain incidence, alterations in immune system, impaired rehabilitation, increased hospital stay or readmissions to the hospital, impaired quality of life, and excessive sedation due to opioid use .There are developments regarding novel analgesic medical treatments and techniques to be employed in preoperative, intraoperative, and postoperative periods to better manage acute postoperative pain (Gordon et al., 2016).

A number of studies have focused on pain treatment in spine surgery, but most studies have focused on primary degenerative conditions in the lumbar spine treated with discectomy, decompression and lumbosacral fusion .Since an increased number of major spinal procedures, including revision surgery can be anticipated, we found it of relevance to assess a multimodal pain treatment strategy in patients undergoing surgery requiring instrumentation (Mathiesen et al., 2013).

While opioids provide effective analgesia, their use can be limited by side effects in the perioperative period (Oderda et al., 2013).

Multimodal analgesia, which combines analgesic drugs from different classes and employs analgesic techniques that target different mechanisms of pain, is recommended in the treatment of acute postoperative and

trauma-related pain because its synergistic effect maximizes pain relief at lower analgesic doses, thereby reducing the risk of adverse drug effects (Polomano et al., 2017)[4].

Aim of the work

To asses and compare the efficacy of using different doses of gabapentin and celecoxib as combination for multi modal analgesia in postoperative pain relieve in patient underwent posterior approach lumbar spine 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 20-60 years old scheduled to undergo elective posterior approach lumbar spine fixation surgery (3 levels or less) done by the same surgeon under general anesthesia, were enrolled in this prospective, randomized, double blinded controlled study.

Preoperative assessment and preparation:-

- A careful medical history was taken.
- General examination including pulse (HR), arterial blood pressure, respiratory rate (RR) and oxygen saturation.
- Physical examination including chest, heart, abdomen, and other systems.
- Routine investigations including:
  - Complete blood picture (Hb, platelet), coagulation profile (PC, PT, INR), renal function test (urea, creatinine), liver function test (AST, ALT, albumin, bilirubin) and random blood sugar.
  - Electrocardiogram (ECG) for patients over 40 years old.

We explained to patients all steps of general anesthesia, and how to evaluate their own pain intensity using the visual analogue score of pain (VAS), explanation of VAS was done, (VAS is consisted of a straight, vertical 10-cm line; the bottom point represented "no pain"=(0 cm) and the top "the worst pain you could ever have "= (10 cm) (Chuangang Peng et al., 2017).

Drugs and tools used in the study:

1. Gabapentin (Gaptin 300 mg Cap, Delta pharma, Egypt)
2. Celecoxib (Celebrex 200mg Cap, phizer)
3. Placebo capsules (empty capsules).
4. Bispecteral index (BIS) (COVIDIEN, Singapora).
5. One touch device for random blood sugar (On call plus).
6. Monitor (UltraviewSL2700, Spacelaps, USA) for (ECG, SPO2 and NIBP).
7. Anesthetic machine ((Datex Ohmeda, GE, USA).
8. Portable pulse oximetry (OLED digital)
9. Mercury sphygmomanometer.

Study patient groups:

Patients were randomized to four groups (25 patients in each group):

- Group **GC** received gabapentin 300mg + celecoxib 200mg 2hr pre-operative and the same combination 6 hr postoperative.
- Group **G** received gabapentin 300mg + celecoxib 200mg 2hr preoperative and gabapentin 300mg 6 hr postoperative.
- Group **C** received gabapentin 300mg + celecoxib 200mg at both 2hr pre-operative and celecoxib 200mg 6hr postoperative.
- Group **O** (placebo) as control group received empty capsules 2hr pre-operative and 6 hr postoperative.

Results

One hundred patients of both gender, ASA I and II ,aged between 20-60 years old scheduled to undergo elective posterior approach lumbar spine fixation surgery 3 levels or less under general anesthesia were enrolled in this pro-spective, randomized, double blinded controlled study in Minia University Hospital. Patients enrolled and randomized into 4 equal groups each group 25 patients.

Patient's Characteristics Data:

As regard Patient's characteristics age, sex, duration of surgery and cause of operation were comparable in all studied groups with p value >0.005.

As shown at Table .

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

	GC (n=25)	G (n=25)	C (n=25)	O (n=25)	p value
Age (yrs) Mean±SD (Range)	 45.7±8.2 (32-60)	 44.7±9.7 (30-60)	 42.4±10.9 (21-61)	 49.5±9.7 (28-60)	 0.077
Sex Male Female	 14 (56%) 11 (44%)	 15 (60%) 10 (40%)	 16 (64%) 9 (36%)	 14 (56%) 11 (44%)	 0.929
Duration of surgery (min.) Mean±SD (Range)	 115.6±25.5 (80-160)	 115.6±26.6 (80-160)	 112.4±15.9 (90-140)	 103.2±12.8 (80-120)	 0.129
Cause of operation • Sensory loss • Motor deficit • Failure of medical treatment	 4 (16%) 10 (40%) 11 (44)	 7 (28%) 9 (36%) 9 (36%)	 5 (20%) 8 (32%) 12 (48%)	 4 (16%) 9 (36%) 12 (48%)	 0.923

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.

During studying we noted that VAS was significantly lower in the three groups (GC, G and C) respectively compared with group O Immediately after recovery, 2nd hr, 4th hr ,6th hr ,8th hr ,10th hr, 12thhr and 24thhr post-operative with P value < 0 .01 Inter group comparison revealed that the three groups (GC, G and C) were comparable regarding to VAS immediately after recovery. But comparison between groups revealed that VAS score was the best in group GC, and worst in group O in 2nd hr, 4th hr, 6th hr, 8thhr, 10th hr, 12thhr and 24th hr post-operative.

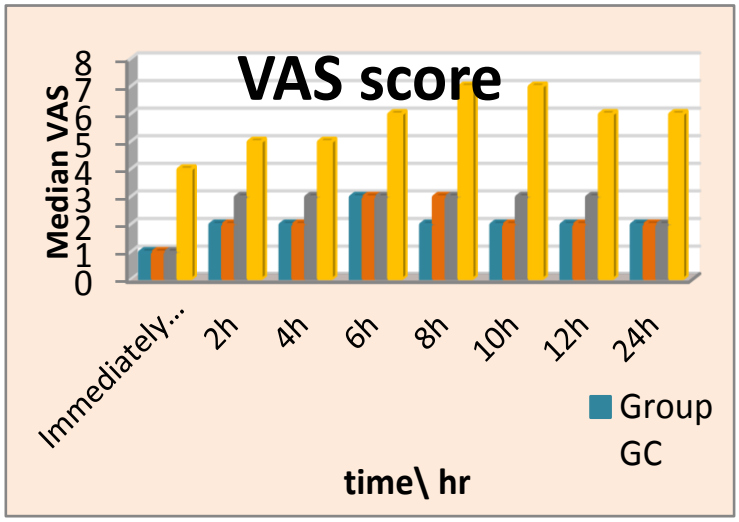

Figure Comparison of postoperative pain score (VAS).

2-Comparison of postoperative VAS scores.

VAS	GC (n=25)	G (n=25)	C (n=25)	O (n=25)	p value	Between groups	
							p value
Immediately after recovery *Median (IQR)*	1 (0-2)	1 (0-2)	1 (0-2)	4 (2-4)	**<0.001***	*GC vs G*	0.890
						GC vs C	0.828
						GC vs O	**0.001***
						G vs C	0.733
						G vs O	**0.001***
						C vs O	**0.001***
2h *Median (IQR)*	2 (1-2)	2 (2-2)	2 (1-3)	5 (5-6)	**<0.001***	*GC vs G*	0.353
						GC vs C	0.424
						GC vs O	**0.001***
						G vs C	0.495
						G vs O	**0.001***
						C vs O	**0.001***
4h *Median (IQR)*	2 (2-2)	2 (2-3)	2 (2-3)	5 (5-6)	**<0.001***	*GC vs G*	0.132
						GC vs C	0.061
						GC vs O	**0.001***
						G vs C	0.592
						G vs O	**0.001***
						C vs O	**0.001***
6h *Median (IQR)*	3 (2-4)	3 (2-4)	3 (3-4)	6 (5-7)	**<0.001***	*GC vs G*	0.534
						GC vs C	0.166
						GC vs O	**0.001***
						G vs C	0.434
						G vs O	**0.001***
						C vs O	**0.001***
8h *Median (IQR)*	2 (2-3)	3 (2-3)	3 (2-3)	7 (5-7)	**<0.001***	*GC vs G*	0.265
						GC vs C	0.074
						GC vs O	**0.001***
						G vs C	0.556
						G vs O	**0.001***
						C vs O	**0.001***
10h *Median (IQR)*	2 (1-2)	2 (2-3)	3 (2-3)	7 (5-7)	**<0.001***	*GC vs G*	0.081
						GC vs C	0.083
						GC vs O	**0.001***
						G vs C	0.927
						G vs O	**0.001***
						C vs O	**0.001***
12h *Median (IQR)*	2 (2-2)	2 (2-2)	3 (2-3)	6 (6-7)	**<0.001***	*GC vs G*	0.185
						GC vs C	0.076
						GC vs O	**0.001***
						G vs C	0.480
						G vs O	**0.001***
						C vs O	**0.001***
24h *Median (IQR)*	2 (2-2)	2 (2-2)	2 (2-3)	6 (5-6)	**<0.001***	*GC vs G*	0.516
						GC vs C	0.062
						GC vs O	**0.001***
						G vs C	0.075
						G vs O	**0.001***
						C vs O	**0.001***

Discussion

Spinal procedures are associated with high level of postoperative pain compared to other surgical procedures and majority of patients report moderate to severe pain, which persists for at least initial 3-4 days. This pain is proportional to the number of operated vertebrae and the invasiveness of the procedure (Devin & McGirt, 2015).

Adequate pain relief is important facet of postoperative care of these patients as these patients had already suffered from preexisting chronic pain that had been treated with conventional analgesics or narcotics. The long-term consumption of analgesics and/or opioids alters pain perception in these patients thereby complicating pain management. Effective pain controls facilitates early mobilization as well as decrease hospital stay (Bajwa & Haldar, 2015).

NSAIDs play a role in pain relief, especially in postoperative pain caused by inflammation. They have demonstrated significant opioid dose-sparing effects, which help in reducing postoperative effects and opioid side effects (Zhifeng Zhang et al., 2017).

Celecoxib is a selective cyclooxygenase (COX)-2 inhibitor, has inhibitory effects on prostaglandins synthesis, both in the spinal cord and peripheral nervous system, and reduces hyperalgesia status after surgical traumas. It is illuminated that compared with conventional nonsteroidal anti-inflammatory drugs, celecoxib has less gastrointestinal side effects and less influence on antiplatelet function with long-term use (Zhou, et al., 2017). Recently, celecoxib has been demonstrated to have analgesic efficacy after spinal surgery, COX-2 inhibitors have been demonstrated to have analgesic efficacy during pain at rest and with movement (Sekiguchi et al., 2015).

Gabapentin used in many studies, gabapentin is a structural feature of gamma amino butyric acid. The mechanism of gabapentin action is to reduce the release of several excitatory neurotransmitters (e.g. glutamate, substance P, calcitonin, noradrenaline, gene-related peptide) by binding to the α2δ subunit of voltage dependent calcium channels (Patel & Dickenson, 2016). Gabapentin has antiallo-dynic, antihyperalgesic properties that decrease the hyperexcitability of dorsal horn neurons due to tissue injury, and anxiolytic effects (Javaherforooshzadeh et al., 2018).

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 multi-modal analgesia with substantial evidence to support efficacy in postoperative patients include gabapentinoids, acetaminophen, keta-mine, non-steroidal anti-inflammatory drugs and regional anesthesia (Kim SI, Ha, & Oh, 2016).

As regard post-operative VAS score in our study it was significantly lower in group GC, G, and C respectively than group O.

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 agree 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. In his 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.

(Mahjoubifard et al., 2016) studied 76 patients scheduled for elective herniorrhaphy were

enroled in this study. Patients were divided into 2 groups; celecoxib group (n=38) received 200mg celexib 2 h pre-operative and placebo group (n=38), Then pain score (VAS score) was recorded in 2nd, 6th, 12th and 24th hours after tracheal extubation. the result was that the mean of the VAS score after 2 hours was 5.7 by placebo but 2.2 by celecoxib with a significant difference (P= 0.003) agree with ours ,the median VAS score in our result after 2 h was 2 at the three groups (GC, G, C) and 5 in the O group. the scores were not different too much after 6 hours (P= 0.3). These non-significant results continued later in cases but in our result after 6 h there was significantly decrease in VAS score in the three groups (GC,C,G) compare with placebo that may be due to using preoperative combination of gabapentin and celecoxib as preoperative preemetive multi-modal analgesia for post-operative pain management.

(Vasigh, Najafi et al., 2016) in this randomized double-blind clinical trial, 114 patients scheduled for elective laminectomy with simple random sampling design divided into 3 groups The patients in the group A (gabapentin) received 600 mg gabapentin two hours before surgery and 300 mg six hours after surgery, group B (celecoxib) received 400 mg celecoxib two hours before surgery and 200 mg six hours after surgery and group C (placebo) received a placebo capsule orally two hours before surgery and six hours after surgery and the VAS was used to determine severity of pain. The pain severity was assessed in the 2, 4, 6, 8, 12 and 24 hours after surgery.At measuring VAS at 2h and 4h post operatively they found that VAS decreasing more in gabapentin than celecoxib without significant difference but with significantly difference in comparison to placebo. In our result we found the same by using combination of both drugs in lower doses than they used. At 6h in his study VAS score still decreasing but in our result there was insignificant increase in VAS in each group. Then after giving postoperative dose of analgesia the VAS at 8hr, 12hr, 24hr were significant decrease in gabapentin and celecoxib respectively ($P < 0.001$, $P < 0.05$). This decreasing in VAS score started at 8th hr in GC group, 10^{th} hr in G group without no decreasing occurred in C group. This difference in result may be related to the difference in doses and different combination which used and the difference in type of operation in our research.

In (Vasigh, Jaafarpour, et al., 2016) they found that VAS in the gabapentin plus celecoxib group was significant lower compared to the placebo and gabapentin group respectively at various intervals , this is in agreement with our study in using gabapentin and celecoxib combination and this is better than using gabapentin alone in higher dose, In their result they found that at 12hr and 24hr VAS score still decreasing in gabapentin plus celecoxib group and gabapentin respectively but in our result VAS didn't decrease more that may be due to different type of operation.

In (Paul et al., 2013) who studied patients who underwent primary total knee arthroplasty Subjects received either gabapentin 600 mg preoperatively followed by 200mg every eight hours for two days or matching placebo and the result was mean pain scores at rest, with passive movement, or with weight bearing were similar in both groups at corresponding time periods for the first three days following surgery this study didn't agree with ours, that may be due to absent of drug combination and different procedure.

In (Waraporn et al., 2011) pain score recorded at 1, 4, 8, 12, 16, 20, and 24 hours post-operatively 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.

We assessed Preoperatively anxiety score and RBS followed by intra operative, hemodynamics (HR, MAP, So2), end tidal isoflurane concentration (lower anesthetic requirement with lower BIS values from 40:50), analgesic requirement, RBS, and till the end of operation. Then during the first 24 hour post-operative, VAS score, hemodynamics (HR, MAP, So2, RR), RBS, time of 1st analgesic request, frequency of analgesic requirement, patient satisfaction score, and complications were recorded.

We conclude that preoperative and post-operative combination of gabapentin 300mg and celecoxib 200mg provide lower pre-operative anxiety score, better intraoperative (hemodynamics, RBS, anesthetic requirement and analgesic requirement), lower post-operative (VAS score of pain, RBS and analgesic requirement) higher patient satis-faction score when compared with using every drug alone or placebo respectively in patients who underwent spine fixation surgery.

Recommendation

Based on the current study we recommend:

1- Usage of preemitive multimodal analgesic with various mechanism of action is more useful in post-operative pain relieve after major surgery.

2- Further studies to test different doses of used drugs.

3- Further studies to objectively assess postoperative pain.

4- Multicenter study may be needed for more accurate evaluation.

5- Further studies to assess chronic post-surgical pain (CPSP) by prolonged time for follow up patients.

References

1. Bajwa, S. J. S., & Haldar, R. (2015). Pain management following spinal surgeries: An appraisal of the available options. Journal of craniovertebral junction & spine, 6(3), 105-110.
2. Bateman, B. T. (2016). Variations in the Use of Perioperative Multimodal Analgesic Therapy. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *124*(4), 837-845. doi:10.1097/ALN.0000000000001034
3. Chuangang, Peng, Li C, Qu J, Wu D. Gabapentin can decrease acute pain and morphine consumption in spinal surgery patients: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 96(15):e6463.
4. Devin, C. J., & McGirt, M. J. (2015). Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional out-comes. Journal of Clinical Neuro-science, 22(6), 930-938.
5. Gordon, D. B., de Leon-Casasola, O. A., Wu, C. L., Sluka, K. A., Brennan, T. J., & Chou, R. (2016). Research Gaps in Practice Guidelines for Acute Post-operative Pain Management in Adults: Findings From a Review of the Evidence for an American Pain Society Clinical Practice Guideline. The Journal of Pain, 17(2), 158-166.
6. Javaherforooshzadeh, F., Amirpour, I., Janatmakan, F., & Soltanzadeh, M. (2018). Comparison of Effects of Melatonin and Gabapentin on Post Operative Anxiety and Pain in Lumbar Spine Surgery: A Randomized Clinical Trial. *Anesthesiology and pain medicine*, *8*(3), e68763-e68763.
7. Kim, S.-I., Ha, K.-Y., & Oh, I.-S. (2016). Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial. European Spine Journal, 25(5), 1614-1619.
8. Ladha, K. S., Patorno, E., Huybrechts, K. F., Liu, J., Rathmell, J. P., & Mathiesen, O., Dahl, B., Thomsen, B. A., Kitter, B., Sonne, N., Dahl, J. B., & Kehlet, H. (2013). A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. European Spine Journal, 22(9), 2089-2096.
9. Mahjoubifard M, Enayati H, Noori N, Mahdy S, Jahangiri Fard A (2016) The Effect of Preemptive Oral Celecoxib on Pain Reduction and Opioid Consumption during Elective Herniorrhaphy. Enliven: J Anesthesiol Crit Care Med 3(1): 001.
10. Mathiesen, O., Dahl, B., Thomsen, B. A., Kitter, B., Sonne, N., Dahl, J. B., & Kehlet, H. (2013). A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. European Spine Journal, 22(9), 2089-2096.
11. Oderda, G. M., Gan, T. J., Johnson, B. H., & Robinson, S. B. (2013). Effect of Opioid-Related Adverse Events on Outcomes in Selected Surgical Patients. Journal of Pain & Palliative Care Pharmacotherapy, 27(1), 62-70.
12. Patel, R., & Dickenson, A. H. (2016). Mechanisms of the gabapentinoids and α2δ-1 calcium channel subunit in neuropathic pain. *Pharmacology Research & Perspectives*, *4*(2), e00205.
13. Pandey, C. K., Sahay, S., Gupta, D., Ambesh, S. P., Singh, R. B., Raza, M., Singh, P. K. (2004). Preemptive gabapentin decreases postoperative pain after

lumbar discoidectomy. Canadian Journal of Anesthesia, 51(10), 986-989.
14. Polomano, R. C., Fillman, M., Giordano, N. A., Vallerand, A. H., Nicely, K. L. W., & Jungquist, C. R. (2017). Multimodal Analgesia for Acute Postoperative and Trauma-Related Pain. *AJN The American Journal of Nursing, 117*(3), S12-S26.
15. Paul, J. E., Nantha-Aree, M., Buckley, N., Cheng, J., Thabane, L., Tidy, A.,Avram, V. (2013). Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial. Canadian Journal of Anesthesia/ Journal canadien d'anesthésie,60(5),423-431.
16. Sekiguchi, H., Inoue, G., Nakazawa, T., Imura, T., Saito, W., Uchida, K., . . . Takaso, M. (2015). Loxoprofen sodium and celecoxib for postoperative pain in patients after spinal surgery: a randomized comparative study. *Journal of Orthopaedic Science, 20*(4), 617-623.
17. Vasigh, A., Jaafarpour, M., Khajavikhan, J., & Khani, A. (2016). The Effect of Gabapentin Plus Celecoxib on Pain and Associated Complications After Laminectomy. Journal of clinical and diagnostic research: JCDR, 10(3), UC04-UC08.
18. Vasigh, A., Najafi, F., Khajavikhan, J., Jaafarpour, M., & Khani, A. (2016). Comparing Gabapentin and Celecoxib in Pain Management and Complications After Laminectomy: A Randomized Double-Blind Clinical Trial. Iranian Red Crescent medical journal, 18(2), e34559-e34559.
19. Waraporn, W., Theerawat, C., Nuj, T., Peteng, S., & Nadhaporn, S. (2011). Combination of gabapentin and celecoxib for analgesia after major orthopedic surgery: a randomized, controlled trial. Asian Biomedicine, 5(1), 101-110.
20. Zhifeng Zhang, Z., Xu, H., Zhang, Y., Li, W., Yang, Y., Han, T., . . . Gao, J. (2017). Nonsteroidal anti-inflammatory drugs for postoperative pain control after lumbar spine surgery: A meta-analysis of randomized controlled trials. *Journal of Clinical Anesthesia, 43*, 84-89.