Section: Anaesthesiology

Original Research Article

A COMPARATIVE EVALUATION OF PRE-EMPTIVE ANALGESIA WITH PRGABALIN PLUS CELECOXIB VERSUS CELECOXIB ALONE IN PATIENTS UNDERGOING TOTAL KNEE ARTHROPLASTY

Binsha K Hamza[1], Madhusudan Upadya[2], Bejoy Abraham[3]

[1]Registrar, Department of Critical Care Medicine, Baby Memorial Hospital, Kannur, Kerala, India
[2]Professor, Department of Anaesthesiology, Kasturba medical college, MAHE, Mangalore, Karnataka, India
[3]Assistant Professor, Department of Anaesthesiology, Sree Narayana Institute of Medical Sciences, Chalakka, Ernakulam, Kerala, India

Received *: 09/10/2026*
Received in revised form *: 08/11/2026*
Accepted *: 21/11/2026*

Corresponding Author:
Dr. Binsha K Hamza,
Registrar, Department of Critical Care Medicine, Baby Memorial Hospital, Kannur, Kerala, India.
Email: binzbinsha@gmail.com

DOI: 10.70034/ijmedph.2026.4.386

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (4); 2569-2574

ABSTRACT

Background: Total knee arthroplasty is one of the most commonly done procedure in orthopaedic field. Post operative pain is one of the most common complications after the procedure. Multimodal analgesia uses different combination of analgesic agents and techniques to provide pain relief. This study aims for a comparative evaluation of pre emptive analgesia with pregabalin plus celecoxib versus celecoxib alone in patients undergoing total knee arthroplasty.

Materials and Methods: A prospective, non-randomized, active controlled trial was conducted at MAHE, India. A total of hundred eligible patients, aged 55-85 years and ASA class 1 and 2 scheduled to undergo elective total knee arthroplasty were selected for the study consecutively after obtaining their written informed consent. These patients were allocated alternatively into two groups. Group PC received a combination of celecoxib 400 mg along with pregabalin 150 mg and Group P received pregabalin 150mg alone. The selected patients received oral tablets 6 hours prior to surgery. Outcome variables including haemodynamic parameters, pain scale, knee functional outcome and mobilization were assessed in post operative period for 24 hours.

Results: In our study there was a significant difference in pain score between both the groups with the p value less than 0.05. The combination group showed a better knee functional outcome as compared with other group. There was early mobility and more patient quality in the combination group. The need for rescue analgesia was also less in the combination group. The hemodynamic variables were normal across all the patients throughout the procedure.

Conclusion: Perioperative use of combination of pregabalin-celecoxib reduces postoperative pain, opioid consumption, opioid-related adverse effects, and is associated with long-term benefits. The combination can be prescribed in clinical practice for better treatment outcomes and fair prognosis.

Keywords: Pre emptive analgesia, total knee arthroplasty, celecoxib, pregabalin.

INTRODUCTION

Knee joint osteoarthritis is a very common cause of dysfunction and morbidity among elderly individuals. Such patients experience significant pain and functional limits during normal routines, resulting in reduced economic productivity and poor standard of life. Even though several conservative treatment methods are accessible for knee osteoarthritis management, the most optimal treatment for end-stage arthritis is total knee arthroplasty. In total knee arthroplasty, prosthesis, i.e. an artificial joint is used to replace the arthritic knee joint. The main indication for total knee arthroplasty is pain, followed by substantial functional limitations of daily activities.[1]

Post-operative pain is the most common complication after TKA that causes delay in mobility and augments the morphine demand that leads to exorbitant cost and increased length of hospital stay. Adequate pain management improves the functional outcome, early ambulation, early discharge and reduces incidence of chronic pain.[2] Multimodal analgesia uses different combination of analgesic agents and techniques to provide pain relief 5. The main objective is to reduce the post-operative use of opioids and their side effects contributing to morbidity like nausea, vomiting, sedation, constipation, sleep disturbance thereby improving quality of life after surgery.

Pre-emptive analgesia is a method of pain management that alleviates the progress of sensory input which intensifies pain post-operatively after TKA. It aims on post-operative analgesia by providing pain control pre-operatively before surgical incision. Pre-emptive approach can reduce the use of other analgesics, boost up analgesic efficacy and perk up the immunity2. Aim of the treatment is to impede the pain sensitizing through hampering pain stimuli and afferent pathway from surgical field. For better post-operative analgesia and faster recovery after TKA, a combination of oral celecoxib and pregabalin can be tried pre-emptively.[3-8]

Celecoxib is a highly selective cyclooxygenase-2 inhibitor which reduces the post-operative hyperalgesia . It prevents formation of inflammatory mediators to reduce pain and inflammation3. Pregabalin, a γ-aminobutyric acid analogue is an oral medication known to have analgesic properties useful for treating neuropathic pain. Pregabalin can be used pre-emptively for reducing surgical pain, to reduce narcotic use, and opioid-related adverse effects. Pregabalin acts against the nociceptive pain mollifying the peripheral mechano-receptors. Pregabalin gradually diminishes central sensitization of the dorsal horn neurons and prevents hyperalgesia.[4]

The principle of pre-emptive analgesia with the combination drug is that it facilitates the attenuation of pain pathways before surgical stimulation and results in reduced post operative perception of pain and need of opioids. The purpose of this study is to compare the pre-emptive analgesia using pre-operative oral dose of combination of celecoxib with pregabalin or pregabalin alone for reducing post-operative narcotic consumption and early ambulation. This study aims not only to relieve patient suffering, but also diminish the side effects caused by the narcotics, particularly in medically compromised patients and thereby reducing hospital cost.

Aim: To compare the combination of Pregabalin and Celecoxib versus Pregabalin alone for pre-emptive analgesia in total knee arthroplasty.

Objectives:

1. 1.To compare hemodynamic parameters between the two study groups
2. To compare alleviation of pain by recording VAS score
3. To compare knee functional outcome
4. To compare mobilization and adherence to enhanced recovery protocols

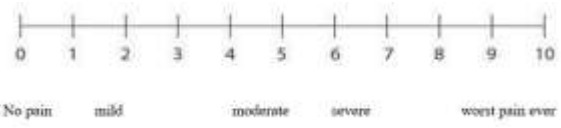
MATERIALS AND METHODS

A prospective, non-randomized, active controlled trial was conducted at our hospitals. The trial was initiated after clearance from the Institutional Ethics Committee. A total of hundred eligible patients, aged 55-85 years and ASA class 1 and 2 scheduled to undergo elective total knee arthroplasty were selected for the study. All the patients underwent detailed pre anaesthetic check-up and investigations as per protocol. The study protocol was explained to the participants and written informed consent was taken before enrolment. The eligible subjects were selected by consecutive sampling. Eligible patients were allocated alternatively to group PC (Patients receiving combination of pregabalin and celecoxib) and group P (Patients receiving pregabalin alone). The selected patients received oral tablets 6 hours prior to procedure. Patients were shifted to the operation theatre next day. Standard monitors such as pulse oximetry, non-invasive blood pressure, electrocardiogram were connected, intravenous access secured. All surgeries were carried out by a skilled orthopaedic surgeon. All patients had undergone the same techniques with subarachnoid block using 15-17 mg heavy bupivacaine(0.5%).

The patients were monitored in the post-operative care unit for the next 24 hrs. Heart rate and rhythm, non-invasive blood pressure (NIBP), oxygen saturation, 3-lead electrocardiogram, respiratory rate were monitored. Hypotension and bradycardia were defined as 20% decrease from the baseline mean arterial blood pressure and heart rate. Patients were watched for any adverse effects and treated.

The assessment of pain was done by visual analogue scale (VAS) in the immediate post op period , 6, 12 and 24 hours after the surgery, in rest and on passive motion. Patients who complained of grade 4 pain at rest or more on 0-10 scale were provided rescue analgesia with intravenous (IV) paracetamol 1g or IV tramadol 50 mg in saline. The first time of requesting analgesia, frequency of administration and total dose consumed during the period of study (24hrs) were recorded in the 2 groups.

Visual Analogue Scale



In order to measure the efficacy, the range of motion is measured using goniometer with knee joint moving actively.

Statistical Analysis: Data was entered in Microsoft Corporation. Microsoft Excel and analysed using SPSS software version 25(IBMTM). Quantitative variables like heart rate, mean arterial pressure, SpO2, pain scores and knee functional outcomes were presented as mean with standard deviation. Qualitative variables like mobility at 2, 4, 6, 12 and 24 hours were presented as frequency and percentages. Bar diagrams were used for graphical representation of data. Independent or student t test was used to compare between heart rate, mean arterial pressure, SpO2, pain scores, knee functional outcomes and mobilization between pregabalin with celecoxib and pregabalin group. Chi square test was used for comparing the mobility at 2, 4, 6, 12 and 24 hours between the groups. A p value of less than 0.05 were regarded as statistically significant.

RESULTS

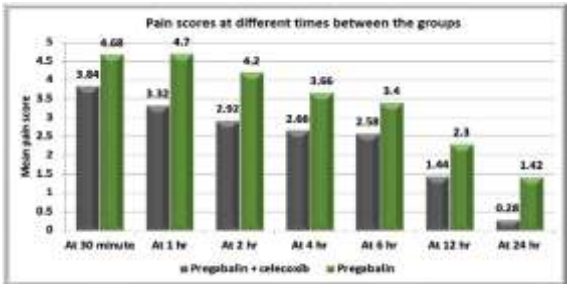


Figure 1: Comparison of pain scores at different point in times between the two groups

In our study the mean pain score was 4 in pregabalin with celecoxib group after 30 minutes of surgery and the same was 5 in pregabalin group. As the time progresses, there was a reduction in pain scores observed in both the groups. All the times there was a significant difference in mean pain scores between the groups and this difference was statistically significant with the p value of less than 0.05. Pregabalin with celecoxib was better in reducing the pain. [Figure 1]

The mean knee functional outcomes score was 48.2 in combination group and 27.4 in single drug group at fourth hour of surgery. The scores had improved as time progresses. There was a significant difference observed between both the groups in our study.

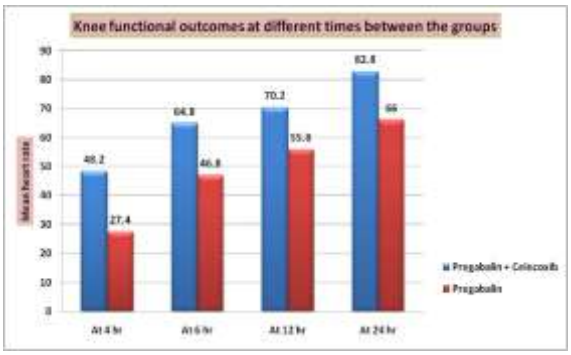


Figure 2: Comparison of knee functional outcomes at different point in times between the two groups

The drug combination groups was performing better in terms of mobility at 2 hours of post-surgery in our study and this difference was statistically significant with the p value of 0.002 [Table 1]. Our study results had showed that as the time increases, both the groups were equally performing but the combination group was better at the initial point itself and showed a better outcome.

Table 1: Comparison of postoperative mobilization between the patients receiving Pregabalin plus celecoxib and pregabalin alone following total knee arthroplasty

Time	Pregabalin + Celecoxib		Pregabalin		P value
	n	%	n	%	
Mobility at 2 hours					
Not mobile	41	82.0	50	100.0	0.002*
Sit	9	18.0	0	-	
Mobility at 4 hours					
Not mobile	24	48.0	34	68.0	0.04
Sit	26	52.0	16	32.0	
Mobility at 6 hours					
Not mobile	7	14.0	1	2.0	0.007
Sit	27	54.0	41	82.0	
Stand	16	32.0	8	16.0	
Mobility at 12 hours					
Sit	12	24.0	5	10.0	0.04
Stand	25	50.0	37	74.0	
Walk	13	26.0	8	16.0	
Mobility at 24 hours					
Stand	14	28.0	18	36.0	0.39
Walk	36	72.0	32	64.0	

*chi-square test

In pregabalin with celecoxib group, 37 (74.0%) did not need any rescue analgesia and 13 (26.0%) needed analgesia. But in pregabalin group, the proportion who needed rescue analgesia was higher when compared to combination group (56% vs 26%). There was a significant difference in the requirement of rescue analgesia between the groups with the p value of 0.002 [Figure 3]. The haemodynamic variables were normal across all the patients through

out the procedure. There was no significant difference between two groups.

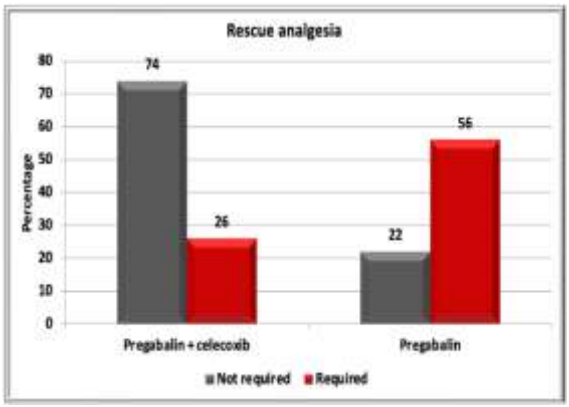


Figure 3: Comparison of postoperative rescue analgesic requirement between the two groups.

DISCUSSION

In this study, the combination of pregabalin-celecoxib was compared to pregabalin alone as pre-emptive analgesia in 100 patients undergoing total knee arthroplasty. It was found that the combination of pregabalin-celecoxib was more efficacious than pregabalin alone in terms of controlling the heart rate, MAP, and SpO2 post-surgery. Also, the combination of drugs leads to better pain scores, knee functional outcomes, and better mobility than pregabalin alone.

For patients with late stage of osteoarthritis of knee, knee replacement can be considered an efficacious, as well as, a cost-effective treatment. However, many experts consider this surgical process a very painful one. Therefore, it is extremely important to ensure adequate and effective pain control after total knee arthroplasty remains. Although several analgesics have been tried, the superior efficacy of one over the other in the real-world setting has not been convincingly proven. Anaesthetists use multimodal analgesia, i.e. the administration of various analgesic agents having different pathways to ensure effective post-operative analgesia. In this regard, pre-emptive analgesia is widely accepted as an adequate supplemental procedure. It has been shown to be a good and acceptable analgesic choice that works by inhibiting the central sensitization of pain in several sites along the pain pathway.[9-12]

As more than 50% of patients undergoing total knee arthroplasty are elderly, pharmacokinetic considerations need to be accounted and thorough evaluations are needed to reduce complications following the administration of analgesic agents. As pre-emptive analgesia, celecoxib (an oral non-steroidal anti-inflammatory drug) and pregabalin (an anti-hyperalgesic and anti-allodynic agent) are used in combination. Their synergistic effects inhibit pain stimuli by multiple mechanisms. Celecoxib acts by the selective inhibition of the cyclooxygenase-2 enzyme, thereby inhibiting prostaglandin biosynthesis, an integral part of the inflammation and pain pathway, resulting in its analgesic, anti-inflammatory, and antipyretic effects. It has better pain control and has less of adverse effects, especially gastro-intestinal effects. On the other hand, pregabalin blocks voltage-gated calcium channels and thereby reduces sensory neuropeptides that include calcitonin gene related peptide and substance P and glutamate release at the synaptic endplate by reducing the influx of calcium. It has a very good analgesic effect and a good safety profile.[13]

The efficacy of the combination of pregabalin-celecoxib, as demonstrated in our study, is in order with previous trials. It was proved that combination drug celecoxib and pregabalin could lower pain sensation and reduce post-operative anxiety in patients undergoing total knee arthroplasty.[14] It was also demonstrated that celecoxib and pregabalin combination could reduce post-operative opioid use for analgesia in total knee arthroplasty patients.[8,15]

According to our study there was an improved recovery and better analgesia for patients who received pregabalin and celecoxib. Lowering of both acute and chronic postoperative pain, as evaluated by visual analogue scale scoring, by the combination of pregabalin and celecoxib as pre-emptive analgesia was demonstrated in other studies as well.[16-18] It was also found that, along with lowering post-operative pain, this combination of analgesic agents could reduce the occurrence of postoperative neuropathic pain. Like in our study, the synergistic effect caused by the addition of celecoxib was more effective than the use of pregabalin alone. Multimodal therapy for postoperative pain management is better than the use of analgesic monotherapy, because of the action of drugs on multiple targets in the pathway of pain.[1]

In patients undergoing knee replacement, it is extremely important to undertake a guided and structured rehabilitation program. For this purpose, early mobilization after surgery results in a better outcome and reduces the duration of hospitalization. Also, the assessment of the knee functionality (range of movement assessment) is required to facilitate early mobilization after surgery. As found in our study, better functional score and early mobilization in the combination analgesic group support the administration of celecoxib-pregabalin in these patients. Hence, it can be regarded that pre-emptive analgesia is looking forward to allow early ambulation of patients who underwent knee replacement surgeries, thereby reducing the incidence of complications like deep vein thrombosis1. We also found that the section of patients with adverse effects was similar in either group, thereby supporting the safety profile of the combination analgesic agents.[1]

Our findings are similar to earlier meta-analyses. A meta-analysis that included seven placebo-controlled randomized controlled trials found that pregabalin use could significantly reduce postoperative opioid (morphine) use in total knee arthroplasty patients. Also, the extent of mobility is also more in pregabalin

celecoxib combination group. Thus, pregabalin was efficacious and safe in patients undergoing TKA.[19] In another meta-analysis, five randomized controlled trials were included. Celecoxib was found to significantly lower pain sensation (reduced visual analogue scale scores), reduced opioid (morphine) requirement after procedure, and improved range of knee movement in those patients undergoing total knee arthroplasty. Thus, celecoxib was efficacious and safe in patients undergoing total knee arthroplasty.[10] These two drugs exhibit synergistic effects when used in combination. In our study, we found that the combination of pregabalin-celecoxib was more efficacious as compared to pregabalin as pre-emptive analgesia in patients total knee arthroplasty patients. The beneficial outcomes in terms of pain management and improved knee functionality were supplemented by the added benefits of improvement of the vital parameters after surgery. Thus, this combination can be preferred as pre-emptive analgesia in total knee arthroplasty patients.

CONCLUSION

Perioperative use of combination drug pregabalin-celecoxib alleviates postoperative pain, reduced use of opioid, opioid associated side effects, and it has prolonged advantages including improved knee functional outcome along with shorter time to achieve efficacious range of motion after the knee replacement. It was found that the combination of pregabalin-celecoxib was more efficacious than pregabalin alone in terms of controlling the heart rate, MAP, and SpO2 post-surgery. Also, the combination of drugs led to better pain scores, knee functional outcomes, and better mobility than pregabalin alone. Thus this combination can be prescribed in clinical practice for better treatment outcomes and fair prognosis.

REFERENCES

1. Lubis, Andri M. T., et al. 'Preemptive Analgesia in Total Knee Arthroplasty: Comparing the Effects of Single Dose Combining Celecoxib with Pregabalin and Repetition Dose Combining Celecoxib with Pregabalin: Double-Blind Controlled Clinical Trial'. Pain Research and Treatment, vol. 2018, Aug. 2018, pp. 1–6. DOI.org (Crossref), https://doi.org/10.1155/2018/3807217.
2. Kien, Nguyen Trung, et al. 'Pre-emptive Analgesia after Lumbar Spine Surgery by Pregabalin and Celecoxib: A Prospective Study'. Drug Design, Development and Therapy, vol. 13, 2019, pp. 2145–52. https://doi.org/10.2147/DDDT.S202410.
3. Li, Jing-wen, et al. 'Postoperative Pain Management in Total Knee Arthroplasty'. Orthopaedic Surgery, vol. 11, no. 5, Oct. 2019, pp. 755–61. DOI.org (Crossref), https://doi.org/10.1111/os.12535.
4. Cho, Eun-Ah, et al. 'The Effect of Perioperative Pregabalin on Pain after Arthroscopic Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial'. Journal of Clinical Medicine, vol. 8, no. 9, Sept. 2019, p. 1426. DOI.org (Crossref), https://doi.org/10.3390/jcm8091426.
5. Jianda, Xu, et al. 'Impact of pre-emptive Analgesia on Inflammatory Responses and Rehabilitation after Primary Total Knee Arthroplasty: A Controlled Clinical Study'. Scientific Reports, vol. 6, no. 1, Sept. 2016, p. 30354. DOI.org (Crossref), https://doi.org/10.1038/srep30354.
6. Reuben, Scott S., et al. 'A Prospective Randomized Trial on the Role of Perioperative Celecoxib Administration for Total Knee Arthroplasty: Improving Clinical Outcomes: Retracted'. Anesthesia & Analgesia, vol. 106, no. 4, Apr. 2008, pp. 1258–64. DOI.org (Crossref), https://doi.org/10.1213/ane.0b013e318165e208.
7. Liu, Jiangfeng, and Fei Wang. 'Preoperative Celecoxib Analgesia Is More Efficient and Equally Tolerated Compared to Postoperative Celecoxib Analgesia in Knee Osteoarthritis Patients Undergoing Total Knee Arthroplasty: A Randomized, Controlled Study'. Medicine, vol. 97, no. 51, Dec. 2018, p. e13663. PubMed, https://doi.org/10.1097/MD.0000000000013663.
8. Feng, James E., et al. 'Total Knee Arthroplasty: Improving Outcomes with a Multidisciplinary Approach'. Journal of Multidisciplinary Healthcare, vol. 11, 2018, pp. 63–73. PubMed, https://doi.org/10.2147/JMDH.S140550.
9. Mishriky, B. M., et al. 'Impact of Pregabalin on Acute and Persistent Postoperative Pain: A Systematic Review and Meta-Analysis'. British Journal of Anaesthesia, vol. 114, no. 1, Jan. 2015, pp. 10–31. DOI.org (Crossref), https://doi.org/10.1093/bja/aeu293.
10. Geng, Xiaoyuan, et al. 'The Efficacy and Safety of Celecoxib for Pain Management After Total Knee Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials'. Frontiers in Surgery, vol. 9, Jan. 2022, p. 791513. DOI.org (Crossref), https://doi.org/10.3389/fsurg.2022.791513.
11. Gong, Li, et al. 'Celecoxib Pathways: Pharmacokinetics and Pharmacodynamics'. Pharmacogenetics and Genomics, vol. 22, no. 4, Apr. 2012, pp. 310–18. DOI.org (Crossref), https://doi.org/10.1097/FPC.0b013e32834f94cb.
12. Xu, Jianda, et al. 'Correction to: The Efficacy of Pre-Emptive Analgesia on Pain Management in Total Knee Arthroplasty: A Mini-Review'. Arthroplasty, vol. 1, no. 1, Dec. 2019, p. 11. DOI.org (Crossref), https://doi.org/10.1186/s42836-019-0013-5.
13. Gordo, Ana C., et al. 'Efficacy of Celecoxib versus Ibuprofen for the Treatment of Patients with Osteoarthritis of the Knee: A Randomized Double-Blind, Non-Inferiority Trial'. Journal of International MedicalResearch,vol.45,no.1,Feb.2017,pp.5974.DOI.org(Crossref), https://doi.org/10.1177/0300060516673707.
14. Geng, Xiaoyuan, et al. 'The Efficacy and Safety of Celecoxib for Pain Management After Total Knee Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials'. Frontiers in Surgery, vol. 9, Jan. 2022, p. 791513. DOI.org (Crossref), https://doi.org/10.3389/fsurg.2022.791513.
15. Lee, Jin Kyu, et al. 'The Effect of a Single Dose of Preemptive Pregabalin Administered With COX-2 Inhibitor: A Trial in Total Knee Arthroplasty'. The Journal of Arthroplasty, vol. 30, no. 1, Jan. 2015, pp. 38–42. DOI.org (Crossref), https://doi.org/10.1016/j.arth.2014.04.004.
16. Munteanu, Ana Maria, et al. 'Is There Any Analgesic Benefit from Preoperative vs. Postoperative Administration of Etoricoxib in Total Knee Arthroplasty under Spinal Anaesthesia?: A Randomised Double-Blind Placebo-Controlled Trial'. European Journal of Anaesthesiology, vol. 33, no. 11, Nov. 2016, pp. 840–45. DOI.org (Crossref), https://doi.org/10.1097/EJA.0000000000000521.
17. Buvanendran, Asokumar, and Jeffrey S. Kroin. 'Multimodal Analgesia for Controlling Acute Postoperative Pain'. Current Opinion in Anaesthesiology, vol. 22, no. 5, Oct. 2009, pp. 588–93. DOI.org (Crossref), https://doi.org/10.1097/ACO.0b013e328330373a.
18. Carmichael, Nicole ME, et al. 'An Intensive Perioperative Regimen of Pregabalin and Celecoxib Reduces Pain and Improves Physical Function Scores Six Weeks after Total Hip Arthroplasty: A Prospective Randomized Controlled Trial'. Pain Research and Management, vol. 18, no. 3, 2013, pp. 127–32. DOI.org (Crossref), https://doi.org/10.1155/2013/258714.
19. Han, Chao, et al. 'Is Pregabalin Effective and Safe in Total Knee Arthroplasty? A PRISMA-Compliant Meta-Analysis of

Randomized-Controlled Trials'. Medicine, vol. 96, no. 26, June 2017, p. e6947. DOI.org (Crossref), https://doi.org/10.1097/MD.0000000000006947.
20. Society, Korean Knee. 'Guidelines for the Management of Postoperative Pain after Total Knee Arthroplasty'. Knee Surgery & Related Research, vol. 24, no. 4, Dec. 2012, pp. 201–07. DOI.org (Crossref), https://doi.org/10.5792/ksrr.2012.24.4.201.