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Research Paper

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PREGABALIN COMBINED WITH CELECOXIB IN COMPARISON TO CELECOXIB ALONE AS PREEMPTIVE ANALGESIA FOR PATIENTS UNDERGOING HIP OR KNEE ARTHROPLASTY.

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Abstract:

Background: Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are widely performed surgical procedures aimed at relieving pain and restoring function in patients suffering from advanced osteoarthritis or other degenerative joint diseases. Pregabalin and Celecoxib, two medications with distinct mechanisms of action, have emerged as valuable components in multimodal analgesic strategies for TKA and THA. We explored the combined effect resulting from the utilization of Pregabalin and Celecoxib in the context of TKA and THA, focusing on their benefits in improving postoperative pain management.

Patients and Methods: We enrolled 87 patients who had TKA and THA between January 2022 and November 2023; they were divided into two groups: The Pregabalin + Celecoxib (group I) and the Celecoxib alone (group II). Two weeks before surgery, each group received an individualized preventive analgesia regimen. Following surgery, the groups' pain scores and side effects were assessed and compared.

Results: The mean pain score of group I was significantly lower than the mean pain scores of (group II) at both 6 (P=< 0.001) and 12 (P=< 0.001) hours postoperatively. Eight cases of dizziness were observed in (group II).

Conclusion: Celecoxib and Pregabalin both before and following TKA and THA reduced pain and enhanced physical function more than Celecoxib alone.

Keywords: Total knee arthroplasty, Total Hip Replacement, Presumptive Analgesia, Pregabalin, Celecoxib

Introduction:

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are considered to be the most popular treatments for advanced joint osteoarthritis (OA) with significant improvement in the quality of life. [1-3] Due to the rising prevalence of knee and hip arthritis, there is a substantial rise in the need for TKA and THA on a global scale. By 2030, 85% more primary procedures are anticipated to be performed. [4]

Following surgery, many patients experience moderate to severe knee pain, even two weeks post surgery. [5] Improved pain control after arthroplasty is associated with quicker recovery, fewer complications, and greater satisfaction among patients. [6, 7] Recent research has demonstrated that tissue inflammatory mediators can repeatedly sensitize pain sensory nerves and cause significant neuropathic pain. [8, 9] Additionally, after leaving the hospital, pain may become more intense, indicationg the coexistence of nociceptive and neuropathic pain mechanisms. [10]

Pre-emptive analgesia is a useful technique for speeding up postoperative recovery and improving pain control, it is administered before the onset of painful stimulation to prevent the development of central sensitization, incisional damage, and inflammation. this strategy is thought to be more successful than giving the treatment after surgery. [11] It is advisable a multimodal analgesic strategy in light of the diverse postoperative pain mechanisms, this treatment approach is based on the synergy of submaximal dosages of analgesics with several mechanisms of action that improve therapeutic potency and lessen side effects. [12] Celecoxib, one of the COX-2 selective inhibitors, can be given safely before surgery because it does not impair platelet function. [13] It is frequently given as a preventative analgesic during the perioperative period of numerous procedures. [14, 15]; some investigations have shown that preoperative Celecoxib treatment can reduce initial postoperative pain and the need for additional analgesics in patients with joint OA who are having arthroplasty. [16, 17] Furthermore, other studies stated that Celecoxib is shown to be more effective at reducing pain when used preoperatively than when administered postoperatively. [18]

Pregabalin is a structurally analogous form of the anticonvulsant medication gamma-aminobutyric acid, which may work by inhibiting voltage-dependent calcium channels throughout the peripheral and central nervous systems, Consequently, it can raise the pain threshold and be applied in the

management of neuropathic pain. [19, 20] Preoperative use of this drug either alone or in combination with Celecoxib, proves to lessen pain and enhance physical performance in patients who underwent arthroplasty. [3, 21-23]

Theoretically, combining Celecoxib and Pregabalin could enhance their analgesic effects after TKA and THA is still necessary. By comparing the pain score and side effects following surgery, our research aimed to assess the efficacy of Pregabalin combination with Celecoxib as TKA and THA preventive analgesia.

Patients and Methods:

Study Design: The study was conducted at AL Basra Teaching Hospital, Basra arthroplasty center, in Basra, Iraq, within the Department of orthopedic surgery. This prospective cohort study spanned from January 2022 to November 2023 and 87 individuals planned for surgery were included, 45 for TKA and 42 for THA were included to compare the effectiveness of Pregabalin combination with Celecoxib versus Celecoxib monotherapy in the treatment of post-operative pain resulting from TKA or THA. To include participants in the current study, a simple random sampling procedure was used.

Inclusion and exclusion criteria:

Inclusion criteria: Patients planned for elective, initial TKA or THA. **Exclusion criteria:** (1) patients with an American Society of Anesthesiologists (ASA) classification of grade 4 or higher, (2) patients with a history of liver and chronic kidney disease, severe cardiopulmonary disease, severe digestive tract disease, and mental illness, (3) patients with an allergy to Celecoxib or Pregabalin (4) patients who had taken Celecoxib or Pregabalin within 2 weeks before surgery, and (5) patients with cognitive impairment.

Study Process:

Preoperative: At least two weeks before surgery, patients were interviewed at their preoperative assessment appointment. After sophisticated history, examination, and appropriate preoperative investigation, they were randomly allocated to one of two therapy groups. Pregabalin (75 mg twice daily) and Celecoxib (100 mg twice daily) were administered to Group 1 (I) for two weeks before surgery. For the same amount of time, tablets of Celecoxib were given to Group 2 (II), and the treatment continued throughout their hospital stay period. The used medications, Celecoxib and Pregabalin, are made in the US by Pfizer company with

the brand names Lyrica and Celebrex, respectively. Patients in both groups were told to stop consuming other painkillers before starting the study drug.

Post-operative: The following were the primary observational indicators during the postoperative period: [24]

1.VAS scores for pain at 6 hours following surgery (pain on a scale of 0 being the lowest to 10 being the highest)

2.Vital signs in the form of blood pressure, pulse rate, and oxygen saturation were assessed postoperatively to check the patient's hemodynamic status.

Ethical considerations: Before gathering data, permission from the Basra Health Directorate was obtained to conduct the study. Following the thorough explanation of the impact and influence of the results on the patient's health, all of the enrolled patients verbally agreed to take part in the study.

Statistical analyses :(SPSS Inc. 26) was used for the statistical analysis. The continuous data were given as mean ± SD, whereas the categorical data were provided as numbers and percentages.

Results:

Socio-demographic characteristics of the studied patients

The total number of the studied patients was 87, with 40 patients on Celecoxib only, and 47 on Celecoxib + Pregabalin. Their ages ranged from 33 years to 73 years. 57.5 % of them were females and 42.5 were males (**Table I**).

Table 1: The characteristics of the studied patients.

Variables		Group I	Group II	
Sex	Male	26	24	42.5
	Female	21	16	57.5
Occupation	Employed	29	8	42.5
	Non-employed	18	32	57.5
Educational level	College	10	4	16.1
	Secondary	10	4	16.1
	Primary	17	20	42.5
	Illiterate	10	12	25.3
Residency	Rural	18	22	46
	Urban	29	18	54
Type of surgery	TKA	29	16	51.7
	THA	18	24	48.3
Variables		Group I	Group II	P value
Age		54.11 ±11.86	58.35 ± 7.68	0.056
Weight		85.91 ± 6.65	87.15 ± 6.43	0.384

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TKA: Total knee arthroplasty, THA: Total hip arthroplasty

Pain and hemodynamic stability between the two groups

Regarding VAS, the study found that VAS scores were significantly lower in Group I compared to Group II (P< 0.001), where the mean value of VAS at 6 hours was (٤,٢٦±0.99) in Group I compared to (7.2±0.4) in Group II, while it was (3.25±0.88) in Group I compared to (5.03±0.8) in the Group II after 12 hours from the surgery (**Table II)**.

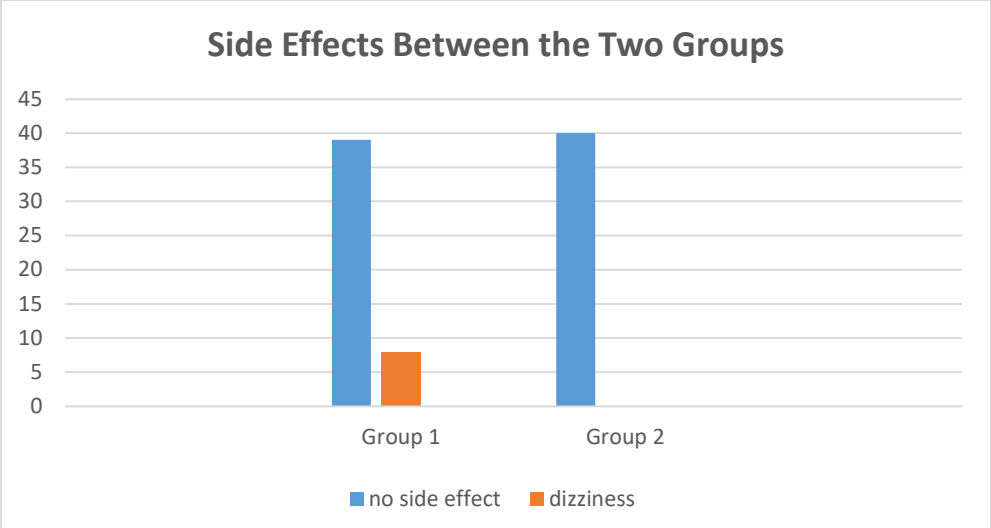
In concern to the hemodynamic status of the patients, the mean value of systolic blood pressure was significantly lower in Group I (121.7±4.8) in comparison with Group II (145±5.06), (P value < 0.001). Regarding pulse rate and SPO2, no significant difference was observed between the two groups **Table II**.

Table II: Pain and hemodynamic stability between the two groups

Group	Group I (No.47) (Celecoxib+ Pregabalin) Mean ± S.D	Group II (No.40) (Celecoxib) Mean ± S.D	P value
VAS score at 6 hours	٤,٢٦± 0.99	٧,٢±0.40	< 0.001
VAS score at 12 hours	٣,٢٥±0.88	٥,٠٣±0.80	< 0.001
Length of hospital stay	1.63±0.36	1.9±0.22	0.012
Systolic Blood pressure	121.7±4.8	145±5.06	< 0.001
Pulse rate	89.2±3.87	90.9±4.13	0.051
SPO2	97.15±1.21	96.5±1.03	0.093

Side effects of the used drugs between the groups

8 cases from group 1 had dizziness as a side effect of treatment, and 39 patients didn't. while all the 40 from group 2 didn't have any side effects (**Figure 1)**.



Side effects of the used drugs between the groups

Discussion

Oral Celecoxib and Pregabalin have both been shown in analgesic studies to significantly reduce postoperative nociceptive and neuropathic pain, respectively. [25, 26] However, there is a paucity of studies comparing the efficacy of their combination to the effects of each medication alone.

In this study, which compared the combination of Celecoxib and Pregabalin with Celecoxib alone, we found that the combination group's perception of pain scores was lower than that of the Celecoxib group. At 6 and 12 hours following the procedure, the combined group's pain scores were consistently lower (P-values < 0.001), suggesting that the combination regimen's analgesic effect was both consistent and long-lasting. Notably, dizziness was experienced by 8 participants in the combination group. Furthermore, apart from differences in systolic blood pressure levels, no significant differences were observed in pulse rates or oxygen saturation between the two groups.

Similar to our findings, patients in Lee et al.'s study received 200 mg of Celecoxib and 150 mg of Pregabalin two hours before TKA, resulting in significantly lower pain levels compared to the control group (Celecoxib alone) at six, twelve, twenty-four, and forty-eight hours post-procedure. [27] Additionally, a study by Carmichael et al. on the perioperative analgesia regimen for patients undergoing THA showed that administering Pregabalin and Celecoxib two weeks before surgery and three weeks afterward

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significantly relieved postoperative pain. Six weeks post-surgery, individuals receiving Celecoxib and Pregabalin scored considerably better on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) for physical function than those in the control group. [3] The combination of Celecoxib and Pregabalin may have beneficial effects on managing central and peripheral hyperalgesia, [28] as well as influence the release of inflammatory mediators. [29] Therefore, we believe that the combination of Celecoxib and Pregabalin, rather than either medication alone, may provide greater value in preemptive analgesia for TKA and THA.

Pregabalin reduces central pain sensitization by suppressing the firing rate of pain fibers and decreasing the release of pain neurotransmitters from the spinal cord, as shown in an animal study conducted by Bannister et al. [30] Conversely, Jianda et al. administered Celecoxib two hours before surgery to TKA patients and discovered that, one week post-surgery, the CRP levels in the preemptive analgesia group were significantly lower than those in the control group. [31] This finding suggests a potential synergistic effect of Celecoxib and Pregabalin on regulating the body's inflammatory response, which may influence pain scores depending on the severity of inflammation.

Previous studies indicate that Pregabalin's effective daily dose ranges from 225 mg to 300 mg. [32] Higher dosages are associated with an increased risk of sedation and dizziness. Although Pregabalin was administered at a lower dose in our study, dizziness was still reported in 8 cases in the combination group. This presents a limitation to its use. Despite this, no other significant side effects were reported in either group.

Hemodynamic stability is a major concern with postoperative analgesia. Fortunately, apart from variations in systolic blood pressure levels, no significant differences were found in pulse rates or oxygen saturation between the two groups. The lower systolic blood pressure in the combination group may be related to the Pregabalin component, as indicated by findings from Res et al., which showed that administering oral Pregabalin before orthopedic procedures improves patients' hemodynamic stability. [33]

This study has two limitations. First, it was confined to a 72-hour assessment following surgery, thus leaving it unclear whether controlling acute postoperative pain promotes long-term knee function recovery

or reduces the risk of chronic pain. Second, as a single-center study, the generalization of results to a broader population may not be accurate.

Conclusion

A comprehensive pain management program involving Celecoxib and Pregabalin, both before and after total knee arthroplasty and total hip arthroplasty, significantly reduced pain and enhanced physical function compared to Celecoxib alone.

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Writing the article 1,2
Critical review, 1, 2
Final approval of the article 1,2
Each author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.
Availability of Data and Material: The corresponding author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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