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# Role of Pregabalin in Pre-Operative and Post-Operative Pain Management of Lower Limb Orthopedic Surgeries

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**Learning Point of the Article:**

- To understand the .mechanism of action of pregabalin.
- To determine whether the pre-operative oral dose of pregabalin is effective in reducing acute post-operative pain.
- To assess the outcome using a Visual Analog Scale scoring system.

## Abstract

**Introduction:** Post-operative pain after orthopedic surgery has remained a challenging problem, which prolongs hospital stay and early rehabilitation. Pregabalin comes under the class of gabapentinoids that have been used in postoperative pain in arthroplasty and spine surgeries but studies regarding its role as pre-emptive analgesia in orthopedic limb surgeries are very few.

Aims: To compare the efficacy of pre-operative pregabalin with a placebo drug in early post-operative pain management for lower limb orthopedics surgeries.

**Materials and Methods:** A randomized double blinded prospective study was undertaken. Sixty patients were enrolled with age between 18 and 70 years and were divided into 2 groups. Group A - received 150 mg of oral pregabalin capsule, and Group B - received matched color empty capsules. Standard spinal anesthesia was given. Breakthrough analgesia was given with an injection of tramadol 50 mg intravenous. Assessment of pain was done with a Visual Analog Scale (VAS) at 6, 12, 24, and 48 h.

**Results:** In comparison to Group B, Group A had a significantly lower postoperative VAS score and required much less breakthrough analgesia within the 1st 24 h after surgery.

**Conclusion:** In orthopedic lower limb fracture surgeries, pre-emptive pregabalin of 150 mg provides adequate postoperative analgesia with relatively few unfavorable side effects.

**Keywords:** Pregabalin, post-operative pain, Visual Analog Scale, tramadol.

## Introduction

Pain is defined as a neuronal response to unpleasant stimuli. The word pain is derived from the Latin word "poena," which means punishment. Pain is a unique, subjective, and complex biopsychosocial process, and neither its existence nor absence can be established. Unrelieved pain causes patients significant physiological and psychological stress. The International Association of Study of Pain describes pain as "an unpleasant sensory and emotional experience that could indicate actual or potential tissue damage" [1].

The complex process of postoperative pain is influenced by both physiological and psychological elements. Tissue damage due to surgery if not treated properly will lead to chronic pain. As it has a significant impact on the functional outcome, proper post-operative pain management following orthopedic surgery remains a critical problem for the surgeon.

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*Author's Photo Gallery*

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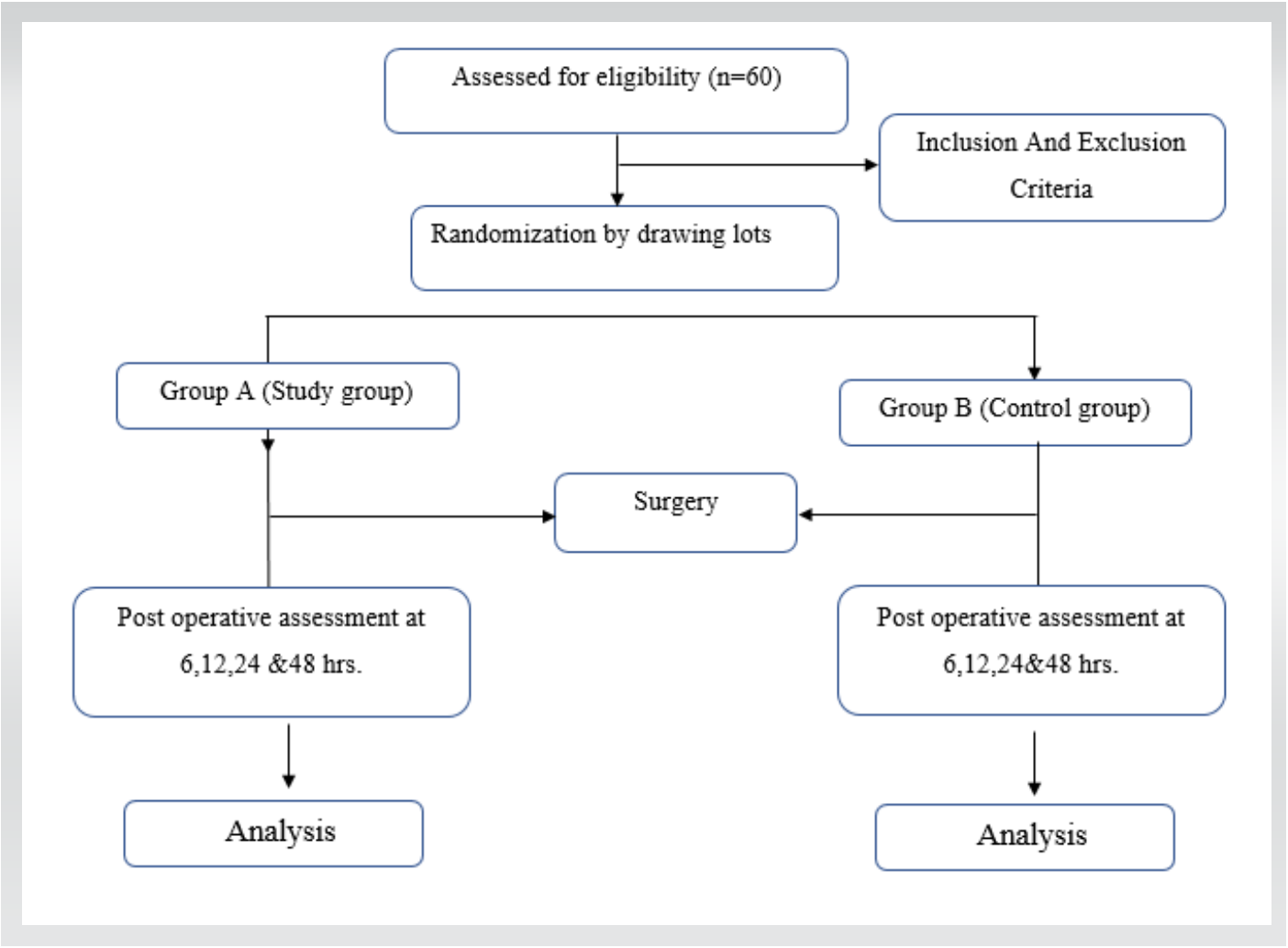


Patient satisfaction, quicker recovery, shorter hospital stays, and lower costs are all associated with effective post-surgical pain treatment. After surgery, postoperative pain is common and can be expected. Preventing and controlling pain are the main objectives of pain management after surgery. In the 1st 24–48 h following surgery, postoperative pain is anticipated to be present consistently, with pain spikes associated with movement, deep breathing, coughing, tachycardia, anxiety, longer hospital stays, patient discomfort, and delayed recovery.

Fundamental elements of pain management include quantifying pain intensity and carefully utilizing analgesics to predict therapy response to optimize functional status and quality of life. Post-operative pain may result from inflammation brought on by tissue damage from the surgical incision, nerve injury from nerve transection, cauterization injury, or when it involves stretching, or compression [2]. Pro-inflammatory mediators such as prostaglandins, interleukins, cytokines, and neurotrophins that are generated as a result of tissue damage help to increase nociceptor sensitivity. In addition, alterations in tissue pH and oxygen tension as well as raised lactate content, have a major impact on peripheral sensitization and spontaneous pain behavior following an incision. Anxiety, tachycardia, hypertension, increased blood sugar, and delayed wound healing are just a few of the systemic impacts that poorly managed postoperative pain can have on the patient [3].

Chronic post-surgical pain, which can appear even after a simple procedure, is linked to psychological stress, despair, and slower healing. As a result, a key aspect of anesthesia delivery must be providing proper post-operative pain control. The basic goals of post-operative pain management in orthopedic surgeries include lowering medication dosage, minimizing adverse effects, and providing the right analgesia. Pre-emptive analgesia is a strategy that involves giving patients medications before surgery in an effort to reduce post-operative pain. It is currently quite popular and has been shown to be effective in doing so. Drugs including opiates, local and regional anesthetics, patient-controlled analgesia, non-steroidal anti-inflammatory drugs, centrally acting medications, gabapentinoids, clonidine, and dexmedetomidine are included in this category.

Hence this study was conducted to determine whether the pre-operative oral dose of pregabalin is effective in reducing acute post-operative pain in patients who undergo lower limb

**Table 1**: Age distribution

| Age in years | Group A | | Group B | |
|---|---|---|---|---|
| | Number | % | Number | % |
| 18–20 | 2 | 7% | 1 | 3% |
| 21–30 | 10 | 33% | 2 | 7% |
| 31–40 | 5 | 17% | 2 | 7% |
| 41–50 | 4 | 13% | 11 | 37% |
| 51–60 | 4 | 13% | 4 | 13% |
| 61–70 | 4 | 13% | 8 | 27% |
| 71–80 | 1 | 3% | 2 | 7% |
| Total | 30 | 100% | 30 | 100% |
| Range | 20–71 | | 18–75 | |
| Mean | 47.1 | | 43.57 | |
| SD | 15.064 | | 17.238 | |

SD: Standard deviation

**Table 2:** Gender distribution

| Group A | | Group B | |
|---|---|---|---|
| Male | Female | Male | Female |
| 23 | 7 | 24 | 6 |

**Table 3:** Duration of surgery

| Duration in minutes | Group A | Group B |
|---|---|---|
| Range | 60–230 | 60–180 |
| Mean | 130.67 | 142 |
| SD | 44.095 | 39.339 |

SD: Standard deviation

**Table 4:** Visual Analog Scale score of Group A versus Group B

| VAS | Drug | N | Mean | SD | Z-value | P-value |
|---|---|---|---|---|---|---|
| 6 h | Group A | 30 | 8 | 0.32 | 6.606 | 0.0005** |
| | Group B | 30 | 8.9 | 0.31 | | |
| 12 h | Group A | 30 | 7.8 | 0.53 | 2.997 | 0.003** |
| | Group B | 30 | 8.3 | 0.6 | | |
| 24 h | Group A | 30 | 5.4 | 0.77 | 3.244 | 0.001** |
| | Group B | 30 | 6 | 0.61 | | |
| 48 h | Group A | 30 | 4.9 | 0.37 | 1.222 | 0.222# |
| | Group B | 30 | 4.6 | 1.16 | | |

** Highly significant at P<0.01 and #No significance at P>0.05

**Table 5:** Total dose of Tramadol administered in 48 h post-surgery

| | Drug | N | Mean | SD | Z-value | P-value |
|---|---|---|---|---|---|---|
| Total dose of tramadol administered in 48 h post-surgery in mg | Group A | 30 | 116.7 | 24 | 5.016 | 0.0005** |
| | Group B | 30 | 156.7 | 36.5 | | |

**Highly significant at P<0.01

orthopedic surgeries under Spinal anesthesia.

## Materials and Methods

This was a randomized control trial study that was conducted in the Department of Orthopedics, Chettinad Hospital and Research Institute, Kelambakkam between May 2022 and February 2024 involving all patients who were scheduled for elective lower limb orthopedic surgeries. All the patients were selected for the research based on criteria for inclusion and exclusion and allotted to the respective groups using randomization.

Sample size calculation (Graph 1)

$N1 = ((\sigma_1)_2 + (\sigma_2)_2 \div K)(Z1\neg\alpha/2 + Z1\neg\beta)\,2/\Delta 2$

N1 - ((64)2 + (64)2 +/1) (1.96 + 0.84) 2/(46)2

N1 = 30

N2 = 30

Total = 60

Δ - (μ2-μ1)

N1 - Sample size of Group 1

N2 - Sample size of Group 2

**Table 6:** Incidence of adverse effects

| Adverse effects | Group A | Group B |
|---|---|---|
| Nausea | 2 | 1 |
| Giddiness | 5 | 1 |

α = Type 1 error (0.05)

β = Type 2 error (0.2)

Z = Critical Z-value

K = Ratio of sample size for Group 2 to Group 1

**Inclusion criteria**

1. Patients undergoing closed/open reduction with intramedullary interlocking nailing procedure for a closed shaft of femur and tibia fractures
2. Age group 18–75 years
3. Elective orthopedic surgeries.

**Exclusion criteria**

1. Known allergy to pregabalin

2. Patient with a known case of hepatic failure
3. Patient with a known case of renal failure
4. psychiatric disorders
5. Chronic pregabalin use
6. History of drug abuse
7. Emergency surgeries.

A standardized protocol was followed for the patients undergoing elective lower limb orthopedic surgeries. 2 h before induction of spinal anesthesia, drug A and drug B were administered. No other pre-medications were permitted.

**Post-operative assessment**

Patients were evaluated for pain intensity, the need for opioid analgesics, and any side effects, such as nausea, vomiting, headaches, and dizziness at 6, 12, 24, and 48 h following surgery. A Visual Analog Scale (VAS) was used to measure post-operative pain. All patients were taught how to use a 10-point VAS, where 0 indicates no pain and 10 indicates acute agony, to describe how much discomfort they were in. Standard analgesia was given post-operatively (injection PARACETAMOL 1 g BD). Patients were given injection TRAMADOL 50 Mg IV for breakthrough pain as soon as the VAS reached 6.

## Discussion

Poor pain management following any major surgery has been associated with low patient satisfaction and may contribute to the development of chronic pain in a significant number of patients.

Orthopedic fractures are associated with severe pain and morbidity due to extensive bone and soft tissue damage and it's further exacerbated by surgery, hence, adequate analgesia is required in the immediate post-operative period for proper pain relief and prevention of various adverse effects associated with it. Recent advances in molecular biology have enhanced the understanding of numerous pain pathways that have led to the application of pre-emptive analgesia.

Pregabalin is a cyclic gamma-aminobutyric acid analog with a specific analgesic effect on neuropathic pain. It has been shown to affect a subset of 2–1 subunit-containing neurons' voltage-sensitive Ca2+ channels. According to the hypothesis, decreasing Ca2+ entrance into the presynaptic neurons through these channels could limit glutamate release, hence lowering neuronal excitability. Pregabalin is recommended as a first-line treatment in cases of neuralgic pain caused by postherpetic neuralgia and diabetic neuropathy. Pregabalin has also been used in the management of generalized anxiety disorders, chronic pain, and partial seizures because it effectively decreases spinal cord neuron overexcitability and regulates the brain's excitatory neurotransmitter activity. Pre-emptive pregabalin has been in the study for its potential role in the management of acute post-operative pain.

According to Beaussier et al. [4], orthopedic surgeries are among the most painful procedures to endure afterward. For this reason, the study was conducted on orthopedic patients. 60 patients were included in this trial and were divided into two groups for lower limb orthopedic surgery under spinal anesthesia: Group A received 150 mg of pregabalin, whereas Group B patients received a placebo. This study is comparable to one done by Akhavanakbar et al. [5] who assessed whether pregabalin pre-operative treatment was effective in reducing post-operative pain following lower limb orthopedic surgery using a similar drug dosage. Jokela et al. [6] discovered that premedication with pregabalin 150 mg improved analgesia in patients undergoing day-case gynecological laparoscopic surgery. The medications were therefore given in this trial before surgery. A 100 mg dose of pregabalin given before surgery, according to Paech et al. [7], did not help to lessen the first post-operative discomfort or hasten recovery after a small procedure affecting only the uterus. Pregabalin 150 mg was administered during gynecological procedures as part of a study by Bafna et al. [1], and it was discovered to be beneficial in lowering acute post-operative pain. In a study by Pandey et al. [8] with 100 lumbar discectomy patients, the researchers found that those who received gabapentin at dosages of 600, 900, or 1,200 mg consistently scored lower on pain scales than those who received placebo or gabapentin 300 mg. This agrees with the study's conclusions.

The medication was given pre-operatively. Based on a study by Bon Sebastian entitled "Effect of oral pregabalin as a pre-emptive analgesic in patients undergoing lower limb orthopedic surgeries under spinal anesthesia," he discovered that a single dose of pregabalin given 1–2 h before surgery significantly reduced post-operative pain scores, post-operative opioid consumption, and opioid-related side effects. The patients in each group received the drugs 2 h before surgery. This is based on a study by Elinor Ben Menachem [9], which found that pregabalin's maximal plasma concentration occurred about 2 h after administration. All of the patients received standard anesthetic care. Both groups shared the same demographic characteristics overall. They were also comparable to the American Society of Anesthesiologists physical status and comorbid conditions. For Group A, the mean operation time was 130.67 min, with a SD of 44, while for Group B, it was 142 min, with an SD of 39 (Table 1). In contrast, the length of surgery in the study by Rajendran et al. [10] was 48.17 min, 46.7 min, and 45.6 min, respectively, for the three groups. Bafna et al.

[1] conducted a similar study on patients undergoing spinal anesthesia for gynecological procedures with surgery times of 56.8, 57.2, and 57.8 min, respectively. The Visual Analog Score was explained to the study participants. VAS ratings were evaluated after 6, 12, 24, and 48 h following surgery. During the 1st 6, 12, 24, and 48 h following surgery in Group A, the mean VAS scores were, respectively, 8.0, 7.8, 5.4, and 4.9. The average VAS scores for Group B were, in order, 8.9, 8.3, 6.0, and 4.6, respectively (Table 2). All of these time points had P-values that were <0.05, which is significant, with the exception of 48 h, where there was no statistical difference between the two groups. Thus the VAS scores were significantly less in both Group A compared to Group B in the early post-operative period of 24 h. This shows that, compared to controls, patients receiving pregabalin premedication have significantly lower mean VAS scores in the 1st 24 h following surgery, but there were no significant VAS score changes after 24 h. This is comparable to the findings of the study by Agarwal et al. [11], which assessed the efficacy of a single 150 mg dose of pregabalin taken before surgery in patients having laparoscopic cholecystectomy. Patients using pregabalin demonstrated a significant decrease in VAS scores during the 1st 24 h following surgery, which is consistent with the findings of this study. In research by Turan et al. [12] including patients following abdominal hysterectomy, gabapentin resulted in significantly reduced VAS scores at 1, 4, 8, 12, 16, 20, and 24 h during both rest and movement.

The average amount of rescue analgesic (tramadol) given throughout the course of 48 h was calculated in this study (Table 3). The average tramadol dosage needed in Group A participants was 110 mg. The dosage needed for Group B was 135 mg. The P-value, which was discovered to be 0.080, is significant. As a result, it was discovered that Group A's overall tramadol intake was much lower than Group B's. However, the average tramadol dosage in Rajendran et al. trial was 200.77 mg in the gabapentin group, 90.5 mg in the pregabalin group, and 386.5 mg in the control group, demonstrating that pregabalin was more effective than gabapentin in lowering opioid consumption following surgery.

The total dose of analgesics (diclofenac) in the 1st 24 h following spinal anesthesia surgery in the trial by Saraswat and Arora [13] was 62.5 mg in Group P (pregabalin-300 mg) and 72.5 mg in Group G (gabapentin 1200 mg), and neither dose was statistically significant. This is consistent with the study's findings. In a research by Pandey et al. [8], it was discovered that the gabapentin group consumed much less fentanyl (221 g) than the placebo group (35 g), with a P = 0.05, in patients having laparoscopic cholecystectomy. Fentanyl consumption was 35% lower in the gabapentin group. In contrast to the findings of Ghai et al. study's, which showed that pregabalin 300 mg, administered orally 1–2 h before abdominal hysterectomy, resulted in a significantly lower post-operative analgesic requirement compared to gabapentin 900 mg and placebo, the findings of this study are different. Pre-operative consumption of diclofenac and tramadol was 250 mg in the placebo group, 152 mg in the pregabalin group, and 170 mg in the gabapentin group.

In this study, Group A patients reported 2 cases of nausea and 5 cases of giddiness, compared to Group B patients who reported 1 case of nausea and 1 case of giddiness. At 6 h following the surgery, Group A experienced more episodes of nausea, but there was no statistically significant difference between the groups in terms of vomiting or dizziness (Table 4). The incidence of adverse effects such nausea, vomiting, fatigue, and dizziness was found to be similar in the Gabapentin group and the pregabalin group in research by Pandey et al. in patients having discectomy. The study by Rajendran et al. revealed that patients on pregabalin or gabapentin experienced no notable negative effects.

The study had limitations, as we used a single pre-operative dose of 150 mg pregabalin 2 h before surgery. However, there is no consensus about the appropriate timing, dose, and duration of the drug. Moreover, we conducted this study in a single hospital; therefore, the generalizability of our findings deserves further investigation in the future. The study entirely focused on tibial and femoral shaft fractures as inclusion groups, other limb surgeries were not included but may include in future studies.

## Results

The study enrolled 60 individuals who were scheduled to undergo femur and tibia nailing surgeries. They were randomly divided into 2 groups of 30 patients each. Approximately 2 h before induction of anesthesia the oral medication was administered. Group A - received 150 mg of oral pregabalin capsule 2 h before surgery and Group B - received a placebo. The patients were induced by standardized spinal anesthesia technique with 12–15 mg of bupivacaine 0.5% injected into the L4-L5 disc space by using a 25-gauge needle and the surgery was performed.

A blind observer was included in the study to evaluate the post-operative pain of patients after surgery. The minimum age in Group A and Group B was 18 years. Group A had a mean age of 47.10 years, while Group B had a mean age of 43.57 years. The average operation time in minutes for the two groups is displayed in Table 1-3, respectively. For Group A, the mean operation time was 130.67 min, with a standard deviation (SD)

of 44, and for Group C, it was 142 min, with an SD of 39. Between the two groups, there was no statistically significant difference (P > 0.05). Thus, the length of surgery for the two groups was comparable.

All patients were assessed for their VAS scores at 6, 12, 24, and 48 h post-operatively. The mean VAS ratings in Group A were, respectively, 8.0, 7.8, 5.4, and 4.9 during the post-operative period of 6, 12, 24, and 48 h. The mean VAS scores for Group B were 8.9, 8.3, 6.0, and 4.6, respectively. With the exception of 48 h, where there was no statistical difference between the two groups, all of these time points had P-values that were <0.05, which is highly significant. This demonstrates that there is a substantial decrease in the mean VAS scores in patients using pregabalin premedication compared to control in the 1st 24 h following surgery, but there were no significant differences in VAS scores observed beyond 24 h (Table 4). All patients who had a VAS score of 6 or above received intravenous (IV) tramadol for post-operative analgesia. Tramadol 50 mg IV was then administered when the VAS score was 6 or higher or at the patient's request. For each patient, the total amount of tramadol needed throughout the post-operative period up to 48 h was calculated. The typical tramadol dosage needed in group A participants was 110 mg. The dosage needed for group B was 135 mg. The P-value, which was discovered to be 0.0005, is quite significant. As a result, it was discovered that Group A's overall tramadol intake was much lower than Group B's (Table 5).

In Group A, there were 12 open reduction cases and 18 closed reduction cases and in Group B, there were 13 open reduction cases and 17 closed cases. In Group A, 2 patients complained of nausea and 5 patients complained of giddiness whereas 1 complained of nausea and 1 complained of Giddiness in Group B is displayed in Table 6.

## Conclusion

From this study patient having lower limb orthopedics procedures under spinal anesthesia, pre-emptive analgesia with pregabalin provides better post-operative pain relief than a placebo.

Pre-emptive pregabalin reduces the need for use of post-operative opioids in the 1st 24 h following surgery. Pregabalin has minimal adverse effects in the early post-operative period.

### Clinical Message

The use of pregabalin as pre-emptive analgesia has better postoperative pain relief within 24 h, which reduces the need for post-operative opioids

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Conflict of interest:** Nil **Source of support:** None

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