The Effect of Magnesium Sulfate Infusion on Postoperative Opioid Consumption in Abdominal Hysterectomy: A Randomised, Double-Blind Trial

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ABSTRACT

Objective: To assess the impact of magnesium sulfate infusion on total opioid consumption following abdominal hysterectomy in a clinical setting.

Study Design: Controlled, randomised, prospective, and double-blind trial.

Place and Duration of the Study: Department of Gynaecology, Giresun Gynaecology and Children's Diseases Training and Research Hospital, Giresun, Turkiye, from November 2023 to April 2024.

Methodology: A total of 48 participants were randomly assigned to two groups: Group M (magnesium sulfate infusion) and Group N (placebo). Participants in Group M were administered a bolus 20 mg/kg $MgSO_4$ in 100 mL of saline over 15 minutes prior to induction, followed by 20 mg/kg/h until skin closure. Participants in Group N received an equivalent volume of saline. The primary outcome was total opioid consumption within the first 24 hours, while secondary outcomes included pain scores, remifentanil use, haemodynamic parameters, and adverse effects.

Results: Postoperative opioid consumption during the first 24 hours was significantly lower in Group M (35.6 ± 15.2 mg) compared to Group N (44.9 ± 14.1 mg), with a p-value of 0.032. Pain scores were also significantly lower in Group M at 24 hours ($p = 0.008$) at rest, at 4 hours ($p = 0.022$), and 6 hours ($p = 0.041$) during movement. No significant differences were observed in remifentanil consumption, haemodynamic parameters, sedation levels, or nausea between the two groups.

Conclusion: The intraoperative administration of magnesium sulphate significantly reduced opioid consumption and pain scores following abdominal hysterectomy. These findings support its use within multimodal analgesia strategies.

Key Words: *Analgesia, Gynaecologic Anaesthesia, Hysterectomy, Magnesium sulfate, Patient-controlled analgesia, Postoperative pain*.

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INTRODUCTION

Abdominal hysterectomy is one of the most commonly performed surgical procedures targeting the female reproductive system and is frequently associated with moderate-to-severe postoperative pain. The invasive nature of the surgery leads to tissue damage and subsequent intensification of the inflammatory response, which may adversely affect the patient's recovery process.

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Recent studies emphasise that inflammation plays a central role in the pathophysiology of pain, highlighting the need for a multidisciplinary approach to effective pain management.[1]

Multimodal analgesia aims to enhance analgesic efficacy while minimising the side effect profile of each medicine through the combined use of agents with differing mechanisms of action. This strategy promotes earlier mobilisation, reduces the length of hospital stay and associated costs, and significantly improves overall patient satisfaction.[2] In modern clinical practice, a core element of multimodal analgesia involves the use of non-opioid analgesics and adjuvant agents alongside opioids.

In recent years, intravenous magnesium sulfate ($MgSO_4$) has emerged as a safe and effective adjuvant in randomised controlled trials and meta-analyses that enhances the efficacy of opioid analgesics and reduces their requirement. Magnesium is thought to exert its analgesic effect by inhibiting N-methyl-D-

aspartate (NMDA) receptors in the central nervous system and regulating calcium channels, thereby suppressing pain transmission and neuroplastic changes.[3,4] Additionally, current literature suggests that magnesium may delay the development of morphine tolerance and contribute to the control of neuropathic pain components.[5,6]

Nevertheless, conflicting findings have been reported regarding the analgesic efficacy of $MgSO_4$ following abdominal hysterectomy. These inconsistencies underscore the need for standardised administration and dosage guidelines. In this context, there has been a growing body of literature re-evaluating the analgesic effects of $MgSO_4$ in relation to various clinical parameters such as opioid consumption, pain scores, side-effect profiles, and patient satisfaction. This growing interest may help clarify the role and optimal use of $MgSO_4$ within multimodal analgesia strategies.

This study intended to provide a more comprehensive analysis of the potential benefits and mechanisms of $MgSO_4$ in postoperative pain management following abdominal hysterectomy. Specifically, an assessment is intended to determine the extent to which $MgSO_4$ contributes to reduced opioid requirements, its influence on the duration and quality of analgesia, and its associated side-effect profile. The findings are expected to support the development of more effective and safer pain management protocols in clinical practice. The objective of the study was to assess the impact of $MgSO_4$ infusion on total opioid consumption following abdominal hysterectomy in a clinical setting.

METHODOLOGY

This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Gumushane University Clinical Research Ethics Committee (Approval No: 2022/1). This study was registered at ClinicalTrials. gov (NCT 05644873). The CONSORT guidelines for controlled, randomised clinical trials were followed (Figure 1).

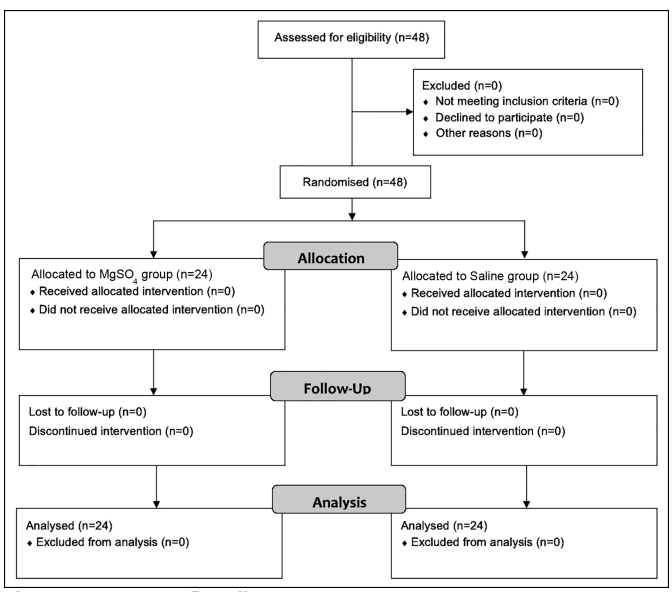

Figure 1: CONSORT flow diagram.

This controlled, randomised, prospective, double-blind trial study was conducted between November 2023 and April 2024. Participants aged 20 to 70 years with American Society of Anesthesiologists (ASA) physical status I-II were included in the study. Exclusion criteria encompassed significant renal, cardiovascular, or liver dysfunction; neuromuscular disorders; the use of beta-blockers or calcium channel blockers; substance abuse; pregnancy or breastfeeding; obesity (BMI >30 kg/m^2); or sensitivity to the medicines used in the protocol or $MgSO_4$. The participants were divided into two groups: Those who received $MgSO_4$ were assigned to Group M, and those who did not receive it were assigned to Group N.

All patients undergoing surgical procedures were subjected to standard anaesthetic monitoring, including electrocardiography (ECG), non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), and bispectral index (BIS). The patients received midazolam at a dose of 0.03 mg/kg for premedication. Anaesthesia was induced using 2 µg/kg fentanyl and 2 mg/kg propofol, followed by the administration of 0.6 mg/kg rocuronium to enable endotracheal intubation, and ventilation was adjusted to maintain $ETCO_2$ at 30-35 mmHg. Anaesthesia was maintained with a target BIS of 40-50 using air/oxygen (50 / 50%), rsevoflurane (1 MAC), and remifentanil. Hypotension was defined as SBP <90 mmHg o a 20% decrease from the preoperative values, and bradycardia was defined as HR <45 bpm. These patients were treated with IV ephedrine and atropine.

In Group M, patients were administered a bolus 20 mg/kg $MgSO_4$ in 100 mL of saline over 15 minutes prior to induction, followed by 20 mg/kg/h until skin closure. Group N received an equal volume of saline solution. The magnesium doses were based on previous studies.[7]

Approximately 30 minutes before the end of surgery, 1 mg/kg tramadol, 1 g paracetamol, and 4 mg ondansetron were administered. The neuromuscular blockade was reversed by the administration of sugammadex at a dose of 2 mg/kg. The patients were extubated once full neuromuscular function was clinically confirmed (head lift, grip strength, tidal volume, and SpO_2 >95%). Patients were transferred to the ward after achieving a modified Aldrete score of >8, with the time recorded. Postoperative evaluations were performed by a blinded researcher.

All patients received 50 mg IV ketoprofen and 50 mg IV ranitidine before surgery. Postoperative analgesia in the ward included IV paracetamol (1 g every 8 hours), IV ketoprofen (50 mg every 12 hours), and a standard patient-controlled analgesia (PCA) device with 5µg /mL fentanyl (bolus dose was set as 10 µg, lockout time was 5 minutes, and one-hour limit was 50 µg). In cases where the numeric rating scale (NRS) pain score was ≥4, rescue analgesia with IV 0.5 mg/kg tramadol (maximum dose 400 mg/day) was administered.

Postoperative pain was evaluated using NRS (0, no pain; 10, worst imaginable pain). For this purpose, patients were informed about the NRS, and the operating principles of the PCA device were explained to them one day before surgery. The sedation level was evaluated using the Ramsay sedation scale (awake, agitated,

and/or crying; awake, calm, and alert; drowsy but responsive to verbal stimuli; drowsy but responsive to glabellar tap; drowsy but responding slowly to glabellar tap; no response to stimuli).

Nausea and vomiting (PONV) were evaluated using the verbal descriptive scale (VDS) (no nausea, mild nausea, moderate nausea, vomiting, and multiple episodes of vomiting).[8] Patients with a nausea-vomiting score of 2 or who were intolerant to nausea were scheduled to receive 10 mg IV metoclopramide.

The heart rate (HR), mean arterial pressure (MAP), and SpO_2 were recorded initially (prior to the administration of $MgSO_4$), one minute after anaesthesia induction, and then intraoperatively at the 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, and 120 minutes, and subsequent measurements were taken every 30 minutes.

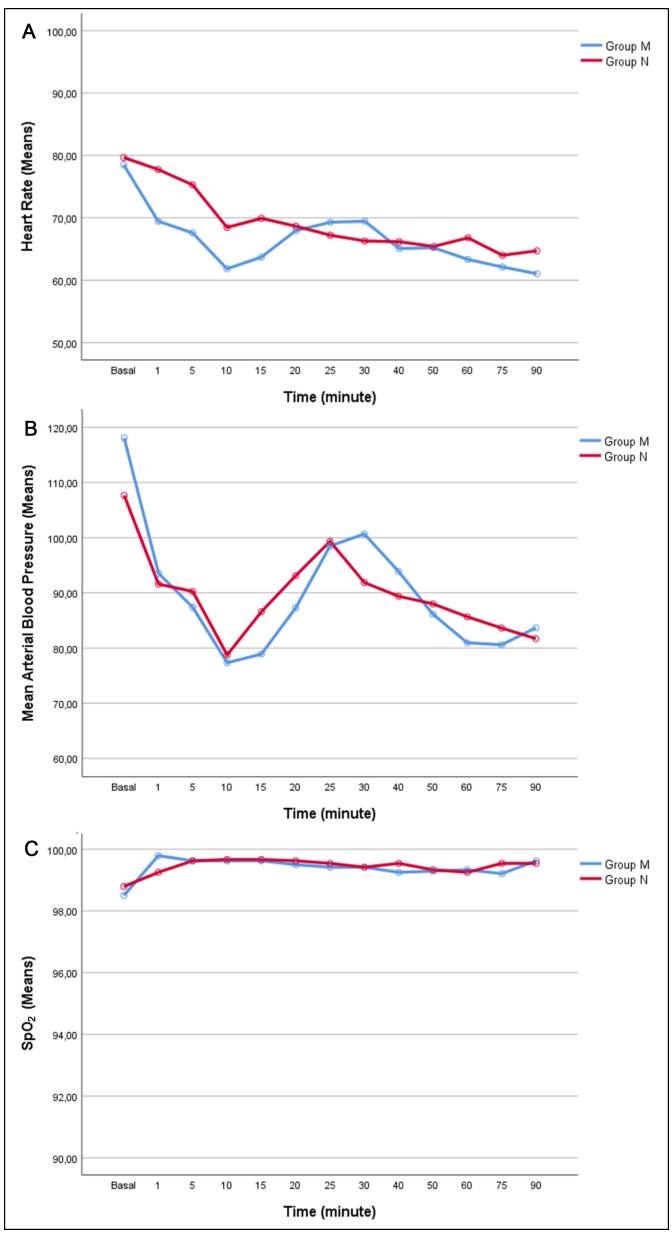

Figure 2: (A) HR according to group and time. (B) MAP according to group and time. (C) SpO_2 according to group and time.

The duration of surgical and anaesthetic procedures, total amount of remifentanil administered, and total amount of intravenous fentanyl administered during the first 24 hours postoperatively were documented. The ward nurse documented the pain, sedation, and nausea-vomiting scores at 30 minutes and 2, 4, 6, 12, and 24 hours postoperatively, as well as the MAP, HR, and SpO_2 on the pain monitoring form.

The primary outcome of this study was the total consumption of opioids in the first 24 hours postoperatively. The secondary outcomes included pain NRS scores (both at rest and during movement), consumption of remifentanil, haemodynamic changes (MAP, HR, and SpO_2), postoperative nausea and vomiting, sedation scores, and any adverse events observed during the first 24 hours postsurgery. Total opioid consumption was calculated as morphine milligram equivalents (MME) using the GlobalRPH opioid equivalency calculator. The conversion factors used were Fentanyl: 0.1 mg IV fentanyl = 10 mg IV morphine, and Tramadol: 100 mg tramadol = 10 mg morphine.

The study included participants divided into two groups, each comprising 24 patients. One group received IV $MgSO_4$ (Group M) and the placebo group (Group N). Participants were randomly assigned to two groups in a 1:1 ratio using the sealed envelope method before arriving at the operating room. Randomisation was performed using codes generated by the computer programme SPSS (version 23.0; IBM, New York, USA). Each participant selected an envelope and was assigned to the group within it. All participants in the study, anaesthesiologists responsible for anaesthesia management, surgeons, and individuals responsible for data collection, were blinded to the group assignments during the study.

Using data from a similar study, calculations were performed in an independent t-test model to determine that a decrease of at least 20% in 24-hour fentanyl consumption compared to the control group was considered statistically significant. A Cohen's D effect size of 1.318 was used in the calculation, indicating that 16 patients in each group were needed for a study power of 95% and a maximum type 1 error of 5%. Considering the possibility of dropout rates, the required sample size was calculated as 20 patients per group, resulting in a total of 40 patients.[9,10]

The data collected in this study were analysed using IBM SPSS Statistics (IBM SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk's test was used to evaluate the normality of data distribution. Continuous variables were reported as mean ± standard deviation or median (interquartile range: 25^{th}–75^{th} percentile), while categorical variables were described using frequencies and percentages. For continuous variables, the independent samples t-test was used when parametric test assumptions were satisfied; otherwise, the Mann-Whitney U test was performed. Categorical variables were examined using the Chi-square test. Repeated measurements at different time points between the groups were analysed using analysis of variance (ANOVA). A Kaplan-Meier curve was plotted to assess the time until the first rescue analgesia, and group comparisons were performed using the log-rank test. A p-value of less than 0.05 was considered statistically significant.

Table I: Characteristics of the patients and opioid consumption in the groups.

Characteristics	Group M (n = 24)	Group N (n = 24)	p-value
Age (year)	55.92 ± 9.15	52.25 ± 9.15	0.172
Weight (kg)	69.58 ± 7	72.33 ± 8.15	0.216
Height (cm)	159.96 ± 4.31	162.21 ± 4.69	0.09
BMI (kg/cm^2)	26.84 ± 2.10	27.46 ± 2.72	0.378
ASA ½	7 (29.2%) / 17 (70.8%)	7 (29.2%) / 17 (70.8%)	1
Duration of surgery (minutes)	168 ± 45	147 ± 38	0.087
Duration of anaesthesia (minutes)	179 ± 45	160 ± 38	0.105
Total remifentanil consumption (µg)	680 ± 401	681 ± 225	0.989
Time to reach modified Aldrete score of 8 (minutes)	10 (8-12)	10 (6-13)	0.609
Total opioid consumption (morphine equivalent, mg)	35.6 ± 15.2	44.9 ± 14.1	0.032

Continuous variables were presented as mean ± SD or median (25-75 percentile), while categorical variables were shown as n (%). Independent samples t-test, Mann-Whitney U test, and Chi-square tests were applied.

Table II: NRS_{rest} and $NRS_{movement}$ scores of groups at different time-points.

Time-points	Group M (n = 24)	Group N (n = 24)	p-value
NRS_{rest}			
30 minutes	6 (3.5-6)	5 (4-7)	0.95
2 hours	4 (3-5)	5 (3.50-5.50)	0.22
4 hours	3 (2-4)	4 (3-5)	0.054
6 hours	3 (2-3)	3 (2.50-4)	0.113
12 hours	2.5 (1-3)	2.50 (2-3)	0.439
24 hours	2 (1-2)	2 (2-3)	0.008
$NRS_{movement}$			
30 minutes	7 (4.5-7)	6 (5.50-8)	0.833
2 hours	5 (4-6)	6 (5.50-7)	0.097
4 hours	4 (4-5)	5.50 (4-6)	0.022
6 hours	4 (3-4)	4.50 (3.50-6)	0.041
12 hours	3.50 (2-4)	3.50 (2.50-4.50)	0.507
24 hours	3 (2-3.50)	3 (3-4)	0.092

NRS = Numering rating scale. Continuous variables were presented as median (25-75 percentile). Mann-Whitney U test was applied.

RESULTS

A total of 48 patients were included and analysed in this study (Figure 1). Demographic, clinical, and surgical data and results were comparable between the groups (Table I). With regard to intraoperative processes and recovery characteristics, the parameters such as duration of surgery, duration of anaesthesia, consumption of total remifentanil, and time to reach modified Aldrete score of 8 were found to be similar between the groups ($p > 0.05$, Table I). Nevertheless, cumulative opioid consumption at 24 hours was significantly lower in Group M (35.6 ± 15.2 mg) than in Group N (44.9 ± 14.1 mg), demonstrating statistical significance ($p = 0.032$, Table I).

Heart rate, mean arterial blood pressure, and SpO_2 were statistically similar between the groups at all time points ($p > 0.05$). Furthermore, changes in heart rate, mean arterial blood pressure, and SpO_2 parametres over time (time × group interaction) were comparable between the groups ($p = 0.275$, $p = 0.985$, and $p = 0.790$, respectively, Figure 2A-C).

The resting NRS score was consistently lower in Group M throughout the study period, with the difference becoming statistical at 24 hours ($p = 0.008$, Table II).

The NRS score during movement were lower in Group M throughout the study period, and this difference was significant at 4 and 6 hours ($p = 0.022$ and $p = 0.041$, respectively, Table II). When patients were assessed for sedation scores and nausea, there were no statistically notable differences were observed between the groups at any time point ($p > 0.05$).

DISCUSSION

The study shows that using $MgSO_4$ during abdominal hysterectomy significantly reduces opioid use and pain scores in the first postoperative 24 hours. These findings align with previous research, confirming the analgesic benefits of $MgSO_4$ as part of multimodal pain management. This study supports its role in lowering opioid consumption and improving pain outcomes.

Multifactorial pain can occur after abdominal hysterectomy, including visceral pain from deeper structures and particularly dynamic pain triggered by coughing or movement.[11] Postoperative pain often requires a combination of medications to manage pain effectively.

Although commonly used opioids can cause problems such as breathing, nausea, and itching. Using adjunctive medications may help to reduce opioid consumption, in turn reducing the occurrence of these side effects.

$MgSO_4$ is a chemical with analgesic properties.[3] It is thought that the medicine works by regulating calcium levels in cells and by blocking some of the brain's sensors. Animal studies support this idea.[12] While some research has suggested that magnesium may improve the effectiveness of opioids and relieve nerve-related pain, other studies have reported conflicting results.[7,8]

Lysakowski *et al*. reached different conclusions regarding whether $MgSO_4$ is a beneficial adjuvant for postoperative anal-

gesia.[13] Their studies suggested that perioperative $MgSO_4$ has a beneficial effect on postoperative pain intensity and analgesic requirements. Similarly, Mavrommati *et al*. concluded that low-dose $MgSO_4$ infusion and protective low-dose boluses are effective adjuvants for perioperative analgesic management.[14] This study also showed that $MgSO_4$ reduces postoperative pain scores, which is consistent with previous studies.[15] However, some studies have reported that $MgSO_4$ does not contribute to postoperative analgesia.[16] This inconsistency may be due to the use of intravenous analgesics in studies showing that $MgSO_4$ improves postoperative analgesia, whereas studies reporting no effect used epidural analgesia. This difference may be explained by the fact that epidural analgesia may mask the analgesic effect of $MgSO_4$.

Albrecht *et al*. found no correlation between the total magnesium dose administered over a 24-hour period and morphine consumption, nor did they identify any advantage of one administration method over another.[6] Similarly, Wilder-Smith *et al*. reported that preoperative intravenous (IV) $MgSO_4$ did not affect postoperative pain scores.[15] Tramer *et al*. also observed that magnesium had no significant impact on postoperative pain scores following abdominal hysterectomy.[17] These findings were consistent with a study on knee arthroscopy, where neither bolus administration nor $MgSO_4$ infusion was deemed sufficient for adequate pain relief.[18] The discrepancies between these studies and the present study may be attributed to variations in surgical type, duration, technique, and the magnesium dosage utilised. However, two recent meta-analyses of randomised controlled trials have concluded that intravenous magnesium significantly reduces morphine consumption, although the reduction in pain intensity was relatively modest in comparison.[6,19]

Tramer *et al*. reported 30% less morphine consumption in abdominal hysterectomy patients in whom magnesium was used.[20] Similarly, many authors have shown a significant reduction in postoperative opioid consumption in different types of surgery.[9] Similar to other studies, this study also found that total postoperative opioid consumption was lower in the group receiving magnesium.

Magnesium has vasodilatory effects, sympathetic blockade, and inhibition of catecholamine release, leading to hypotension and bradycardia. The effects of magnesium on haemodynamic parameters have been investigated in several studies.[20-22] Ryu *et al*. reported that magnesium significantly reduced MAP and HR during intravenous anaesthesia.[21] Seyhan *et al*. and Tramer *et al*. found no differences in haemodynamic parameters between groups.[10,20] Duley *et al*. observed no adverse effects in the first 24 hours despite the use of high-dose magnesium (28 g) in pre-eclamptic women.[23] No difference in haemodynamic parameters was observed between the two groups.

Shulz-Stubner *et al*. reported reduced remifentanil and mivacurium consumption with intraoperative magnesium sulfate administration.[24] Similar findings have been reported in many studies.[11] However, Seyhan *et al*. did not observe a difference in remifentanil consumption and attributed this to the target-controlled propofol infusion.[10] In this study, remifentanil consumption was similar between the groups, probably due to infusion adjustments based on haemodynamic changes. There were no haemodynamic differences between the groups that might have influenced the use of remifentanil.

The positive effect of magnesium on postoperative comfort and sleep patterns may be due to its sedative ability. This is an expected finding. Magnesium is classified as a CNS depressant. However, the literature on this issue is conflicting.[25] In this study, although sedation scores were not different between the groups, early postoperative calmness was more evident in the magnesium group. However, postoperative sleep quality and patient satisfaction were not assessed.

This study has limitations. First of all, the sample size was small. Additionally, magnesium levels in the serum or cerebrospinal fluid were not measured. However, as most magnesium is intracellular (99%), plasma magnesium levels may not reflect total body magnesium levels, limiting the correlation between them.

CONCLUSION

Intraoperative administration of $MgSO_4$ during abdominal hysterectomy significantly reduced postoperative pain scores at 4 and 6 hours and decreased cumulative opioid consumption without significant adverse events. These findings support the inclusion of $MgSO_4$ in multimodal analgesia protocols for abdominal surgeries. Further research is warranted to explore its broader applications and long-term efficacy, especially in diverse surgical populations and with varying analgesic protocols.

ETHICAL APPROVAL:
This study was approved by the Gumushane University Clinical Research Ethics Committee (Approval No: 2022/1). This study was registered on Clinicaltrials.gov (NCT05644873).

PATIENTS' CONSENT:
The authors declared that this study does not contain any personal information that could lead to the identification of the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
IT, ET: Study conception, design, and preparation of the manuscript.
IT, DY, FAB, SOT: Data collection.
ET: Analysis and interpretation of the results.

IT, ET: Drafting of the work, discussion, and literature review. All authors approved the final version of the manuscript to be published.

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