The Effect of Addition of Magnesium Sulfate on Neutrophil/lymphocyte Ratio in Patients Undergoing Lower Abdominal Surgery Under General Anesthesia

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Abstract
Background: Magnesium sulfate is one of the common adjuvants to general anesthetics. Limited number of clinical studies has been done to evaluate the Effect of adding magnesium sulfate to general anesthesia on Neutrophil to lymphocyte Ratio (NLR). Therefore, this study assessed these effects in patients undergoing lower abdominal surgery.
Objectives: This study mainly aims to evaluate the Effect of adding magnesium sulfate to general anesthetics on NLR and its relation to postoperative pain assessment using the VAS score.
Patients and methods: The prospective randomized controlled, double-blind clinical trial involved 60 female patients (age 40-60 years) of American Society of Anesthesiologists (ASA) physical status I- II who were scheduled for elective lower abdominal hysterectomy under general anesthesia and divided into two groups 30 patients in each group (group S and group M). In group (M), magnesium sulfate 50 mg/kg in normal saline with a total volume of 100 ml as loading over 20 minutes given before induction of anesthesia followed by 10 mg/ kg/ hour till the end of the surgery, in group (S) 100 ml of 0.9% NaCl as loading over 20 minutes given before induction of anesthesia followed by 0.1 ml/kg/hour till the end of surgery. Blood samples were withdrawn for NLR calculation, and postoperative pain assessment was done using VAS Score.
Results: There was a statistically significant decrease in postoperative NLR in group (M) compared to group (S) at 4 and 8 h. with *p*-value =0.001. As regards pain assessment using VAS, there was a statistically significant decrease in group (M) compared to group (S) at baseline and 4 h. postoperatively with P value-0.001.
Conclusion: Intravenous magnesium sulfate administered preoperatively in female patients over 40 years old undergoing lower abdominal hysterectomy at dosages of 50 mg/kg decreased postoperative N/L ratio and decreased postoperative pain.
Keywords: Magnesium sulfate; Neutrophil/lymphocyte Ratio; NLR; General Anesthesia; Lower abdominal surgery.
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Introduction

Garcea and his colleges and Bhatt and others found in their study that neutrophil to lymphocyte ratio (NLR) used as a simple way to predict the outcome of patients suffering from cancer and stable coronary artery diseases (**Garcea et al., 2011; Azab et al., 2012**). Surgical stress and anesthetic technique cause changes in NLR.(**Kim et al., 2010; Proctor et al., 2011; Keizman et al., 2012**).

Proctor and kahramanca and their colleges discovered in their studies that anesthetic methods, surgical operations and surgical trauma could affected NLR, and the average value is found to vary in different populations (**Proctor et al., 2011; Kahramanca et al., 2014**). The changes in neuroendocrine due to the effects of anesthetic techniques caused changes in NLR; moreover, analgesia in patients who cannot express pain especially in adult patients, patients with decreased mental status or patients with endotracheal tube. (**Ishizuka et al., 2012**). Surgical trauma initiates acute response to limit infection and tissue injury and begin the process of tissue healing. (**Bhat et al., 2013**).

The changes that occur in the white blood cell count as lymphopenia accompanies neutrophils could be an easy indicator of the inflammatory response which was already used in other circumstances because it is simple and cheap indicator of inflammation (**Masuda et al., 2012; Chen et al., 2015**). NLR has commonly been used in for various mortality, morbidity, and prognosis studies as an indication for inflammation because it is modest, low-priced, and easy to use (**Masuda et al., 2012**). Many studies suggest the role of magnesium sulfate for treatment of diverse clinical conditions such as prevention of eclamptic fits and as tocolytics, treatment of constipation, treatment of some arrhythmias especially with hypomagnesemia, and in patients with severe resistant asthmatic attack.(**Wang et al., 2013**) .Since the use of magnesium sulfate in anesthesia in the beginning of 1996, magnesium has drawn consideration in anesthesia and pain management.(**Lu and Nightingale, 2000**). In this study, we engrossed on the anti-inflammatory properties of magnesium sulfate. The primary outcome of this study is to assess the effect of adding magnesium sulfate to general anesthetics on NLR and its relation to postoperative pain in patients scheduled for elective lower abdominal hysterectomy surgery. In contrast, the secondary outcome included the effects of magnesium sulfate on mean arterial blood pressure, heart rate, and postoperative complications like hypotension, hypertension, bradycardia, nausea, and vomiting.

Patients and Methods

The Medical Ethics Committee, Faculty of Medicine, South-valley University accepted a prospective randomized, double-blind clinical trial (No. 537 On 12-22 /code AIP029/MED/SUV). This study started in September 2019 and ended in May 2022; 60 participants were eligible for this study. Written agreement explained and signed by each patient after explaining all the relevant details about this clinical trial. The study involved female patients (age 40-60 years) of American Society of Anesthesiologists (ASA) physical status I- II who were going to do elective lower abdominal hysterectomy under general anesthesia separated into two groups of 30 patients in each group (group S and group M).

Exclusion criteria: Patients with recent infection, hepatic disease or hepatic enzyme dysfunction, renal disease, endocrine disease including diabetes mellitus, hypertension, allergy to study drugs, blood transfusion in the past week or need for blood transfusion during or after surgery, operation longer than 2 hours and patient refusal.

Randomization was done by a computer-generated random table; patients were allocated into one of two groups, and the group assignments were kept in opaque envelopes, which were seen just after the enrolment of the patients. Neither the doctor "investigator" nor the participant "patient undergoing lower abdominal surgery" was aware of patient sharing or the drug used. The study drug was set by one of the anesthesia supervisors (not involved in the process, observation, or in data gathering). The calculation of NLR is trusted to one of the anesthesiologists who are blinded to the group. Group (M): Magnesium sulfate 50 mg/kg in ordinary saline with a whole volume of 100 ml as loading over 20 minutes was given before initiation of anesthesia, followed by 10 mg/ kg/ hour till the end of the surgery. Group (S): 100 ml of 0.9% NaCl as loading over 20 minutes was given before initiation of anesthesia, followed by 0.1 ml/kg/hour till the end of surgery.

All patients underwent complete checkups before start of anesthetia (according to ASA guidelines), including a full history and physical and systemic checkups. They were kept NPO (nothing per mouth) 6-8 hours for solid food and 2 hours for water and fluids. Basal blood pressure, heart rate, and SpO_2 readings were recorded, complete blood count (CBC) with differential leukocytic count was done, and the patient was educated about using the Visual analogue scale (VAS). 20 G IV line was inserted.

No premedication was given; Intraoperative monitoring items included noninvasive blood pressure (NIBP), heart rate, electrocardiography (ECG), pulse oximetry, and end-tidal CO_2. Pre-induction hemodynamic parameters were recorded. The study solutions were started according to the previously described protocol; then general anesthesia was encouraged with propofol (2 mg/kg) IV followed by atracurium 0.5 mg/kg IV and fentanyl 1 ug/kg. After 3 minutes, intubation was done. Anesthesia was maintained with oxygen 50%, atracurium 0.1 mg/kg and 1 MAC Isoflurane, which will be titrated to maintain adequate depth of anesthesia and maintained hemodynamic parameters not less than 20% of basal readings. When the surgery ended, muscle relaxant was reversed by intravenous atropine 10 μ g/kg and neostigmine 0.05 mg/kg. In both groups, hemodynamic parameters and SpO2 were continuously monitored and noted every 5 min till the end of surgery. Intraoperative intravenous fluid directed by hemodynamic variations and intraoperative blood loss. Intraoperative hypotension (blood pressure drops more than 20% below baseline readings) treated with IV fluids and decreased anesthesia level if possible, and inotropes, intraoperative hypertension or tachycardia treated with increased depth of anesthesia with fentanyl and/or inhalational anesthetics, intraoperative bradycardia treated with atropine 0.1 mg/kg.

Postoperatively, patient shifted to post-anesthesia care unit, and intravenous fluids, antibiotics and other medications were managed according to usual formal protocol. Pain is treated with paracetamol 15mg/kg intravenously every eight hours, ketorolac 30 mg IV every 12 hours, and nalbuphine given in a dose of 10 mg on demand if the visual analogue scale (VAS) score is four or more. The severity of pain was measured via 10 visual analogue scale, where 0 denotes to no pain and 10 denotes to the worst pain ever experienced.

Assessment Parameters

Age, weight, height, ASA, type of operation, duration of operation and anesthesia duration. Mean arterial blood pressure and heart rate recorded in the holding area after the study solutions administration, 10 minutes till ending of the operation and every 20 minutes in PACU. The patient's blood samples were withdrawn for CBC with differential leukocytic count preoperatively, 4, 8 and 12 hours after surgery. NLR may be calculated by (NLR = Absolute Neutrophil Count (ANC) / Absolute Lymphocyte Count (ALC)). Pain score and analgesic consumption were recorded immediately after surgery, 4, 8- and 12 hours postoperative. Intra and postoperative complications.

Primary outcome: The primary outcome of this study was to assess the effect of intravenous magnesium sulfate with general anesthesia on NLR and its relation to postoperative pain in patients scheduled for lower abdominal hysterectomy surgery. **Secondary outcome;** The secondary outcomes of the study include the effects of magnesium sulfate on mean arterial blood pressure, heart rate and postoperative complications like hypotension, hypertension, bradycardia, nausea and vomiting.

Statistical analysis

Sample Size: The sample size was calculated according to a previous study (**Kim et al., 2011**). Assuming the mean difference of 3.0 with an alpha error of 0.05 and the power of the study of 0.95, twenty-five patients would be included in each group. Five patients were added to each group to compensate for those who cannot complete the whole study.

Data analysis: Data was analyzed using SPSS 22 and Microsoft Excel. Tests including Shapiro-Wilk for normality distribution, chi-square, Fisher exact, independent t-test, Mann Whitney U to compare data between both groups according to the type of data, and Kaplan-Meier were applied to compare time to first analgesic request. Significance was set at $p<0.05$.

Results

There were no statistically significant variations between both groups as regards patient's demographic and clinical data (age, weight, height, BMI, ASAI-II, Type of operation, operative duration and anesthesia duration), (**Table.1**).

Table 1.Patients' demographic and clinical data

Variables	Group (S) (n=30)	Group (M) (n=30)	p-value
Age (years)	51.6 ± 3.8	50.6 ± 4	0.312
Weight (kg.)	73.6 ± 8	72.9 ± 9.3	0.733
Height (cm.)	166 ± 6.9	166.7 ± 5.7	0.643
BMI	26.7 ± 1.9	26.1 ± 2	0.263
ASA I/II	10/20	9/21	0.781
Type of operation:			
• **Abdominal hysterectomy**	27	22	0.241
• **Subtotal hysterectomy**	2	6	
• **Fibroid**	1	2	
Operative duration (minutes)	97.7 ± 21.8	98.3 ± 12.1	0.896
Anesthesia duration(minutes)	132.2 ± 23.1	122.8 ± 13	0.934

Data stated as mean (SD). *P* value < 0.05 was considered significant result

As regard to N/L R, at baseline time, mean N/L R were 3.3 ± 0.6 in group (S) 3.4 ± 0.6 in group (M), respectively (P = 0.554). After 4 hours, in group (S), the mean N/L R was 7.2 ± 2.5 and in group (M) was 3 ± 1.2 there were statistically nonsignificant changes between both studies groups. After 4 hours N/L R in group (S) was 7.2 ± 2.5 and in group (M) was 3 ± 1.2. Comparison between both groups presented a statistically significant decrease in group (M) related to group (S) with P value = 0.001. After 8 hours N/L R in group (S) was 5.6 ± 1.9 and in group (M) was 4.3 ± 1.2, and there was a statistically significant decrease in group (M) with P value = 0.003, (**Table.2**).

Table 2.N/L Ratio

N/L Ratio	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline	3.3 ± 0.6	3.4 ± 0.6	0.554
After 4 hours	7.2 ± 2.5	3 ± 1.2	0.001*
After 8 hours	5.6 ± 1.9	4.3 ± 1.2	0.003*
After 12 hours	5.1 ± 1.8	4.8 ± 1.2	0.519

Data stated as mean (SD). *P* value < 0.05 was considered significant result

As regard VAS in postoperative times, at baseline postoperative value of the mean of VAS score in group (S) was 4 (3-5) and in group(M) was 2 (2-5). There was a significant decrease statistically in group (M) compared to group (S) (P value = 0. 001). After 4 hours postoperative value of the mean of the VAS score in group (S) was 3 (1-3) and in group (M) was 2 (1-4). There was a significant decrease statistically in group (M) compared to group (S) (P value = 0.001), (**Table.3**).

Table 3. Pain assessment using VAS Score

VAS score	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline (postoperative)	4 (3-5)	2 (2-5)	0.001*
After 4 hours	3 (1-3)	2 (1-4)	0,001*
After 8 hours	1 (1-3)	1.5 (1-3)	0.168
After 12 hours	3 (2-4)	2 (2-4)	0.987

Data stated as mean (SD). *P* value < 0.05 was considered significant result. *: the significant difference was observed compared between groups.

Regarding the total nalbuphine dose and median first analgesic request, the total nalbuphine dose in mg was given to both groups postoperative. In group(S), the median dose for a total of nalbuphine 10 mg (0-20) the median dose in group (M) was 5mg (0-10). Both groups had statistically insignificant changes (P value = 0.634). As regards the median first analgesic request, the estimated time median (range) in hours were 6.5 (6-7.5) hours in group (S) and the estimated time median (range) in hours 8 (6-9) hours in group (M) with p-value=0.014, (**Table.4**).

Table 4.Total nalbuphine dose and median first analgesic request

Variables	Group (S) (n=30)	Group (M) (n=30)	p-value
Total nalbuphine(mg); median (range)	10 (0-20)	5 (0-10)	0.634
First analgesic request hours; median (range)	6.5 (6-7.5)	8 (6-9)	0.164

Data stated as mean (SD). *P* value < 0.05 was considered significant result

Intra operative mean arterial blood pressure(mmHg), there were significant statistically differences in intraoperative mean arterial blood pressure (mmHg) among group (S) and group (M) after injection of the magnesium sulfate at times of ,10, 20, 30,40,50,60,70 minutes intraoperative (P value=0.001), (**Table.5**).

Table 5. Intra Operative Mean Arterial Blood Pressure (mmHg)

Intraoperative Mean arterial blood pressure (mmHg)	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline	90.5 ± 3.1	89.4 ± 2.6	0.158
After the injection of the study solution	93.3 ± 3.6	87.4 ± 4.2	0.001*
After 10 minutes	78.3 ± 4.4	74 ± 3.9	0.001*
After 20 minutes	78.5 ± 2.9	74.1 ± 3.9	0.001*
After 30 minutes	78.8 ± 3.5	73.3 ± 3.5	0.001*
After 40 minutes	79.2 ± 3.4	74.4 ± 3.7	0.001*
After 50 minutes	78.9 ± 4.1	74.3 ± 4	0.001*
After 60 minutes	78.7 ± 4.8	73.7 ± 3.9	0.001*
After 70 minutes	80.4 ± 4.5	76.2 ± 5.1	0.001*
After 80 minutes	82.9 ± 5.9	80.4 ± 5.3	0.094
After 90 minutes	85.4 ± 6.5	82.7 ± 6.7	0.137
After 100 minutes	87.6 ± 7.6	85.5 ± 9.2	0.481

Data stated as mean (SD). *P* value < 0.05 was considered significant result. *: the significant difference was observed compared between groups.

Postoperative mean arterial blood pressure (mmHg), there were no statistically significant differences in postoperative mean arterial blood pressure (mmHg) between group (S) and group (M) at all times of the postoperative study (P value > 0.05), (**Table.6).**

Table 6. Post- Operative Mean Arterial Blood Pressure (mmHg)

Postoperative Mean arterial blood pressure (mmHg)	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline	93.4 ± 2.4	91.3 ± 6.6	0.112
After 20 minutes	95.1 ± 2.6	92.5 ± 6.6	0.049
After 40 minutes	94.1 ± 2.6	92.5 ± 6.8	0.251
After 60 minutes	93.5 ± 2.6	91.4 ± 6.5	0.109
After 80 minutes	93.7 ± 2.5	91.4 ± 6.6	0.082
After 100 minutes	92.7 ± 2.8	90.6 ± 6.6	0.107
After 120 minutes	92.2 ± 2.3	89.2 ± 6.7	0.024

Data stated as mean (SD). *P* value < 0.05 was considered significant result
*: the significant difference was observed compared between groups

Intra Operative Mean Heart Rate (Beats/Minutes), there were statistically significant differences in intraoperative mean intraoperative heart rate(b/m) between both groups after injection of the magnesium sulfate,10, 20, 30,40,50, and 60 minutes intraoperative (P value=0.001), (**Table.7**).

Table 7. Intra Operative Mean Heart Rate (Beats/Minutes)

Intraoperative Heart Rate (beat/minutes)	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline	79.9 ± 4.2	80.5 ± 3.2	0.535
After the injection of the study solution	83.6 ± 4.4	77.7 ± 5.9	0.001*
After 10 minutes	69.3 ± 4.2	63.7 ± 4.6	0.001*
After 20 minutes	68.8 ± 4.3	63.6 ± 5.2	0.001*
After 30 minutes	68.4 ± 5.5	63.5 ± 4.9	0.001*

After 40 minutes	69.7 ± 5	63.7 ± 3.9	0.001*
After 50 minutes	69.5 ± 5	64.2 ± 4.68	0.001*
After 60 minutes	69.1 ± 6	63.9 ± 4.9	0.001*
After 70 minutes	69.2 ± 6.6	66.2 ± 5.8	0.076
After 80 minutes	73.2 ± 6	70.2 ± 5.8	0.053
After 90 minutes	76 ± 8.1	72.6 ± 6.7	0.095
After 100 minutes	78.2 ± 8.3	75.5 ± 9.8	0.404

Data stated as mean (SD). *P* value < 0.05 was considered significant result. *: the significant difference was observed compared between groups.

Postoperative mean heart rate (b/m), there was no statistically significant alteration in postoperative mean heart rate (b/m) between group(**S**) and group(M) at all times of the postoperative study (P value > 0.05), (**Table.8**).

Table 8.Post- Operative Mean Heart Rate (Beats/Minutes)

Postoperative Heart Rate. (beat/minutes)	Group (S) (n=30)	Group (M) (n=30)	p-value
Baseline.	87.2 ± 2.8	87.1 ± 4.9	0.949
After 20 minutes	89.4 ± 3.3	87.7 ± 6.4	0.212
After 40 minutes	87.6 ± 5.3	86.4 ± 6.9	0.454
After 60 minutes	86.5 ± 6.9	85.6 ± 7.4	0.628
After 80 minutes	86.7 ± 4	84.8 ± 7.8	0.242
After 100 minutes	86.3 ± 5.3	84.7 ± 4.4	0.472
After 120 minutes	85.6 ± 3.8	84.7 ± 4.4	0.382

Data stated as mean (SD). *P* value < 0.05 was considered significant result.*: the significant difference was observed compared between groups.

Postoperative complications, regarding nausea; seven patients suffered postoperative nausea in group (S) and four in group (M). There was a no statistically significant variations between both groups (p-value =0.731). Two patients in each group suffered from vomiting, and there was a statistically insignificant between both groups (p-value =1); these patients were treated by intravenous ondansetron. Regarding hypotension, only one patient in group (M) had hypotension and no one in group (S) with statistically insignificant differences between both groups (p-value =0.492). These patients were treated by intravenous saline only. Only one patient in each group suffered from bradycardia intra-operatively, with a statistically insignificant difference between both groups (p-value =0.55); these patients were treated with intravenous atropine. As regard tachycardia, there were five patients in group (S) and two patients in group (M) intra-operative, with statistically insignificant between both groups (p-value =0.424); the increased depth treated these patients of anesthesia, (**Table.9**).

Table 9 .Complications

Complications	Group (S) (n=30)	Group (M) (n=30)	p-value
Nausea	6 (20%)	4 (13.3%)	0.731
Vomiting	2 (6.7%)	2 (6.7%)	1
Hypotension	0 (0%)	2 (6.7%)	0.492
Bradycardia	1 (3.3%)	1 (3.3%)	0.55
Tachycardia	5 (16.7%)	2 (6.7%)	0.424

Data stated as number (%) of patients. *P* value < 0.05 was considered significant result

Discussion

In pregnant and non-pregnant women, the increase in "Neutrophil-to-Lymphocyte Ratio" (NLR) and "Platelet-to-Lymphocyte Ratio" (PLR) detected in blood cell counts test which gives evidence about systemic inflammation. (**Yazar et al., 2015; Stojkovic et al., 2019; Zheng et al., 2019**). "Systemic Immune-Inflammation Index" (SII) encouraged by neutrophil, platelet and lymphocyte , all these indices are detected easily from blood test counts and provide information about the present inflammatory state.(**Zhong et al., 2017; Tanacan et al., 2020**). Due to the action of Magnesium sulfate as anti-inflammatory and analgesic effect, it is used as an adjuvant drug with general anesthesia. Very few studies have been done to assess the effect of addition magnesium sulfate to general anesthesia on NLR. So, our study was directed to assess these effects in patients scheduled hysterectomy lower abdominal surgery.

The main aim of this study was to assess the effect of intravenous magnesium sulfate on general anesthesia on NLR and its relation to postoperative pain in patients undergoing abdominal hysterectomy surgery.

The results of this study showed nonsignificant changes between the studied groups regarding demographic criteria (age, weight, height, BMI), ASA, duration of operation and type of operation. The results of our study agree with the results of Atar and coauthors, they found that in their study there was insignificant changes in demographics between their groups (P>0.05) (**Atar et al., 2021**).

Concerning NLR, a comparison between both groups after 4 hours presented a statistically significant decrease in group (M) compared to group (S) with P value = 0.001. After 8 hours, N/L R in group (S) was 5.6 ± 1.9 and in group (M) was 4.3 ± 1.2, and there was a statistically significant decrease in group (M) with P value = 0.003. This study was the first study to assess the effect of preoperative intravenous magnesium sulfate on NLR in healthy patients scheduled for elective lower abdominal hysterectomy. In our study, the NLR in group **(S)** increase may be due to several factors. like the effects of general anesthesia with propofol. Hasselager and his colleagues studied the effect of sevoflurane versus propofol during propofol anesthesia on NLR in healthy volunteers and they concluded in their results that there was transient lymphopenia, and this decrease in lymphocyte counts during propofol anesthesia due to propofol and the decreasing in lymphocyte number leads to decrease in NLR. (**Hasselager et al., 2022**).

Ren and coauthors in their study, they concluded that propofol had been T-cell responses which play a key role in peri-operative anti-infection and (**Ren et al., 2010**). Min discovered in his study that lymphopenia-induced homeostatic proliferation which is characterized by transient lymphopenia. (**Min, 2018**). A study by Kallioinen and colleagues showed in their study that the uses of propofol in general anesthesia induced T-cell stimulation. So, according to these studies, propofol causes a decrease in lymphocyte counts when used for anesthesia, which causes an increase in the postoperative NLR which occurred in results of our study. Surgical stress is considered as an another factor which causes increase in postoperative NLR. (**Kallioinen et al., 2019**). Tabuchi and his colleagues studied the effects of general anesthesia and surgical stress on neutrophils count and functions. They studied 10 patients scheduled for elective spine surgery. They founded that the count of neutrophil begins to increase after the start of surgery and got the peak level 3 hours after surgery; the results of our study agree with this study. (**Tabuchi et al., 1989**). Surhonne and his colleagues compared the effect of neuro-axial anesthesia and general anesthesia on NLR, they concluded that a significantly lesser changes in NLR and a decrease in basal total leukocyte count (TLC) in neuro-axial anesthesia than general anesthesia. Their studies showed that surgical stress results in a decrease in cellular resistance, rise in TLC and a drop in the lymphocyte count in the postoperative period which can rise the chance of infection. accordingly, surgical stress causes increase in NLR. (**Surhonne et al., 2019**).Other studies by Takahashi et al and Dovšak et al concluded that surgery stress causes a profound inflammatory reaction that causes an increase in NLR, and this result supports explains our results.(**Takahashi et al., 2006; Dovšak et al., 2018**).

Postoperative pain is another factor which increases the postoperative NLR, Turgut and colleagues' in their retrospective study, they evaluated preoperative and postoperative NLR in 140 patients scheduled for orthognathic surgery. The patients were scheduled into two groups: first group with an NLR level were two or above and the second group those with an NLR below two. They observed that the analgesic requirement of the first group was significantly high. They concluded that there is a correlation of high NLR with increased postoperative pain.(**Turgut et al., 2017**). This result can explain our study's, that the increase in the postoperative NLR in group(S) compared to group (M). So, these factors mentioned before propofol, surgical stress and stimulation of inflammatory cascade and postoperative pain were the causes of the increase in postoperative N/L ratio in group (S) in our study and there was a decrease in NLR in group (M) due to preoperative i.v. magnesium sulfate.

According to the study by Von and his colleagues they concluded that the i.v. magnesium sulfate is regularly shared with 12 adrenoceptor agonists for tocolytic therapy, on lymphocyte cyclic AMP manufacture, extracellular magnesium and blood calcium concentrations.They studied sixteen fit volunteers received i.v. magnesium sulfate 1 g h-1 over 8 h. and seven had an intravenous NaCl (18 mg h-1) as control. They found a significant increased lymphocyte counts led to decreased NLR in magnesium sulfate group, the outcome of this study supported the results of our study. (**Von et al., 1993**). Sugmioto and his colleagues investigated the effect of magnesium sulfate in vivo and in vitro on maternal immune reaction. They concluded that magnesium sulfate affected general inflammation by varying cytokine creation. (**Sugimoto et al. 2012**). da Silva and others studied magnesium sulfate role on immunomodulatory changes of mesenchymal stem cells. They concluded that there were decreases in the levels of IL-1β and IL-6, with IL-10 and amplified PGE2 with magnesium sulfate.(**da Silva Lima et al., 2018**). These studies explains the effect of magnesium sulfate on inflammatory responses, and this causes a decrease in NLR, which is supported by our study. Orgul and coauthors demonstrated in their study that after starting magnesium sulfate there were increase in all NLR, PLR and SII. **(Orgul et al., 2021**). This study results disagrees with our results and this may be due to they did their study on pregnant women and earlier studies exposed that NLR and "Platelet-to-Lymphocyte Ratio" (PLR) are increased with the changed inflammation in pregnant women. (**Yazar et al., 2015; Stojkovic et al., 2019; Zheng et al., 2019; Orgul et al., 2021**). Onsrud and thorsby stated that, physiologic stress causes increase number of neutrophils and decrease the number of lymphocytes, and increased cortisol levels increase the neutrophil count and decrease the lymphocyte count, so the increase of cortisol levels lead to increase NLR.(**Onsrud and Thorsby, 1981**). Leukocytosis and lymphopenia occurred because of endogenous catecholamines which increased in the body due to surgical stress. (**Benschop et al.,**

1996). The effects of magnesium sulfate as an anti-stress can fully explain the decreased N/L ratio in our study.

Concerning Pain assessment using the VAS Score, our study results showed that at baseline postoperative value of the mean of the VAS score in group (S) was 4 (3-5) and in group(M) was 2 (2-5). There was a significant statistically decrease in group M compared to group S (P value = 0. 001|). After 4 hours postoperative value of the mean of the VAS score in group (S) was 3 (1-3) and in group (M) was 2 (1-4). There was a significant statistically decrease in group (M) compared to group (S) (P value = 0.001). The results of this study agree with the results of Yazdi and coauthors, in their study they observed that a decrease in pain levels after 3 h in major abdominal surgery due to magnesium sulfate, and without side effects.

They observed a reduction of opioids 24 h after surgery and concluded that magnesium sulfate acts as physiological inhibitor of calcium channels; without explanation for pain relief remains. They explained the decrease of pain sensation may be due the movement of calcium into the cell and may act as an antagonist to the NMDA receptor. (**Yazdi et al., 2022**) In agreement with our results, Benhaj and his colleagues concluded that the use of magnesium sulfate intravenous with general anesthesia leads to analgesia postoperatively in abdominal surgery. (**Benhaj et al., 2008**). A study by Taheri and coauthors observed that the use of IV magnesium sulfate 15 minutes before the induction of general anesthesia, decreased pain postoperatively in the first day after the abdominal hysterectomies. The results of Taheri study agree with the results of our study.(**Taheri and Haryalchi, 2015**).

As regard Intra-operative mean arterial blood pressure (mmHg), our results showed that there were significant statistically differences in intra operative mean arterial blood pressure (mmHg) between group (S) and group (M) after injection of the study solution at times 10, 20, 30,40,50,60,70 minutes intraoperative (P value=0.001). Operative Mean Heart Rate (Beats/Minutes) in our results showed there were significant statistically differences in intraoperative mean heart rate(b/m) between group (S) and group (M) after injection of the study solution,10, 20, 30,40,50, and 60 minutes intraoperative (P value=0.001). Post-Operative Mean Heart Rate (Beats/Minutes), there was no statistically significant difference in postoperative mean heart rate (b/m) between group(S) and group(M) at all times of the postoperative study (P value > 0.05). The results of this study agree with the results of Honarman and coauthors, they studied MgSO4 in dose of 30 mg/kg or 40 mg/kg, IV compared to 50 mg/kg IV, and they concluded that MgSO4 in doses of 30 mg/kg or 40 mg/kg reduce cardiovascular instability related to laryngoscopy and tracheal intubation compared to 50 mg/kg IV.(**Honarmand et al., 2015**). Our results coincide with those of Jee and his colleagues, they studied the effect of 50mg/kg of magnesium sulfate over 2–3 mints on hemodynamic responses induced by pneumoperitoneum. They observed that there was an increase in HR and decrease in systolic and diastolic arterial pressures in magnesium group compered to control group and they concluded that the decrease in blood pressure may due to inhibiting the release of catecholamines and vasopressin by MgSO4. (**Jee et al., 2009**),. Magnesium sulfate was known to have a relaxing effect on vascular smooth muscles so it attenuated arterial pressure increase during laparoscopic cholecystectomy. (**Delhumeau et al., 1995**). Moreover, in support of our results, Kalra and colleagues studied the effect of 50mg/kg MgSO4 and 1μg/kg clonidine on 120 patients scheduled for elective LC, and they observed that magnesium sulfate leaded to attenuation of hemodynamic response. (**Kalra et al., 2011**). Atar and coauthors in their study disagree with our study; their results showed no significant changes in mean arterial pressures and heart rates and this may be due that their study was done on rates not on human . (**Atar et al., 2021**).

Recommendations

1- Further studies on large sample sizes emphasize our conclusion
2- Further studies on the effect of magnesium sulfate on NLR at different ages and sexes.
3- Further Study the Effect of magnesium sulfate on NLR on different types of operations.
4- Postoperative evaluation time should be longer than 12 hours.

Limitations of the study

1- This study was done on one type of operation, which limited the number of patients,
2- The duration of operations was less than 2 hours, which excluded many patients from the study.
3- Several blood samples from the patients led to the refusal of many patients to enter the study protocol.
4- Short postoperative observation times.

Conclusion

In conclusion, intravenous magnesium sulfate administered preoperatively in female patients over 40 years old undergoing lower abdominal hysterectomy at dosages of 50 mg/kg decreases N/L ratio. Also, magnesium sulfate decreases postoperative pain by regulating the flow of calcium into the cell. It may also serve as an adversary to the NMDA receptor and attenuated the increase in arterial pressure and heart rate changes by inhibiting catecholamine release from adrenal glands and reducing levels of serum epinephrine and causing a decrease in the atrial contraction, bradycardia, and vasodilatation.

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