

**Original article:**

**Analgesic effect of magnesium sulphate as an adjuvant to levobupivacaine in lower abdominal and pelvic surgeries under epidural anaesthesia : A randomized double blind controlled interventional study**

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**ABSTRACT**

**Introduction:** Epidural anaesthesia is commonly used technique for providing surgical anaesthesia with post-operative analgesia.

**Aim:** to evaluate the post-operative analgesic effect of Magnesium sulphate added to levobupivacaine in epidural anaesthesia for lower abdominal and pelvic surgeries.

**Method:** Hospital based, randomized, double blind, controlled, interventional study conducted on 60 patients of 20 to 60 years undergoing lower abdominal and pelvic surgeries and fulfilling inclusion and exclusion criteria, randomly distributed 30 patients to group A (Magnesium sulphate and Levobupivacaine Group) and 30 in group B (Levobupivacaine Group) in general surgery OT and gynaecological surgery OT Department of Anaesthesiology at SMS Medical College and Attached Group of Hospitals, Jaipur with due permission from institutional ethics committee and Research Review Board and with written informed consent.

**Results:** Levobupivacaine with MgSO<sub>4</sub> group took less time (11.70±1.06 min) to achieve sensory block than Levobupivacaine group (17.50±0.86 min) (p<0.05). Onset of motor block was faster in levobupivacaine with MgSO<sub>4</sub> group (15.57±1.55 min) than levobupivacaine group (22.70±1.29 min) (p<0.05). VAS score was higher in levobupivacaine group as compared to levobupivacaine with MgSO<sub>4</sub> group (p<0.05). Levobupivacaine with MgSO<sub>4</sub> group had prolonged post operative analgesia than levobupivacaine group (p<0.05). Hemodynamic parameters at different time intervals and incidence of postoperative complications were not statistically significant.

**Conclusion:** the addition of MgSO<sub>4</sub> to levobupivacaine in epidural anaesthesia has dual effects on the anaesthetic and analgesic profiles.

**Keywords:** Epidural anaesthesia, Levobupivacaine, MgSO<sub>4</sub>.

**Introduction:**

Epidural anaesthesia is commonly used technique for providing surgical anaesthesia with post-operative analgesia in lower abdominal, lower limb, pelvic and vascular surgeries where complications are very less compared to spinal anaesthesia. Also there is no limitation for the duration of surgery if an epidural catheter is in place. It can also be used as a modality for post-operative pain relief.<sup>1</sup> Management of acute pain following surgery has been one of the major concerns in anesthetic practice. Epidural anaesthesia using long acting local anesthetics is safe, familiar, inexpensive technique and it provides postoperative analgesia, yet the need of more prolonged postoperative analgesia has led to the use of different adjuvants to epidural local anesthetics.<sup>2</sup> Levobupivacaine is a relatively new

long-acting local anesthetic that has been produced to address the issue of cardiovascular and neurological toxicity following inadvertent intravascular injections. The three-dimensional structure of local anesthetic molecules forms two enantiomeric molecules that exist in two different spatial configurations. The differential affinity of these enantiomers for sodium, potassium, and calcium channels results in a significant reduction of neurological and cardiac toxicity of the S-enantiomer in comparison to the R-enantiomer. With the increasing usage potential of levobupivacaine for anaesthesia and analgesia, especially in the ultrasound-guided peripheral blocks and labor analgesia, it is required to have the latest evidence-based knowledge about pharmaco-clinical profile of this drug.<sup>3</sup> Magnesium is the fourth most common cation in the body and has a key role in hundreds of physiologic processes. Among the numerous actions of magnesium, the blockade of N-methyl-D-aspartate (NMDA) receptor and calcium channel has an important meaning to anaesthesia. The normal range of magnesium in plasma is 0.7-1.1 mmol/L (1.4-2.2 mEq/L). Hypomagnesemia can occur frequently, especially after surgery such as abdominal, orthopedic and cardiac operation.<sup>4</sup>

When magnesium was used intraoperatively, many researchers reported that it reduced the requirement for anesthetics and/or muscle relaxants. In terms of postoperative analgesia, intraoperative magnesium during surgery can reduce opioid consumption in the first 24 h postoperatively, and to a lesser extent, pain scores.<sup>5</sup>

Researches are still running to find the optimum adjuvant with the most satisfying analgesia and the least side effects, as the currently researched adjuvants are associated with side effects such as nausea, vomiting, respiratory depression, pruritus, urinary retention, sedation, bradycardia, and hypotension.<sup>6</sup> Thus, we have planned to evaluate this randomized double-blind controlled study to assess the post-op effect of MgSO<sub>4</sub> with levobupivacaine in epidural anaesthesia during lower abdominal surgeries on postoperative analgesia.

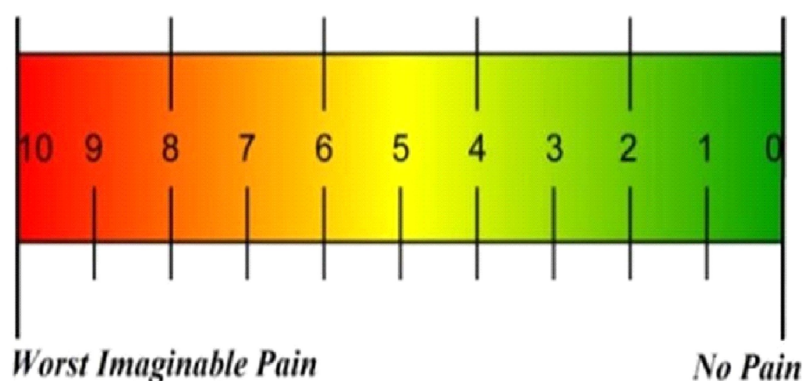
**Aim:** The aim of the study is to evaluate the post-operative analgesic effect of Magnesium sulphate added to levobupivacaine in epidural anaesthesia for lower abdominal and pelvic surgeries.

#### **Method:**

A hospital based, randomized, double blind, controlled, interventional study, conducted on Sample of 30 cases in each group calculated at 95% confidence interval and 80% power to verify the expected difference of 141(+ 21.6) minutes in time duration for need of first rescue analgesia in both groups in general surgery OT and gynaecological surgery OT Department of Anaesthesiology at SMS Medical College and Attached Group of Hospitals, Jaipur with due permission from institutional ethics committee and Research Review Board and with written informed consent. Two groups were made **Group A** (Magnesium sulphate and Levobupivacaine Group): - Patients received Injection 15 ml of a mixture of 14 ml levobupivacaine 0.5%, 0.5 ml magnesium sulphate 10%(50mg), and diluted with 0.5 ml 0.9 NaCl at induction to make a total volume and **Group B** (Levobupivacaine Group): —Patients received Injection 15 ml of a mixture of 14 ml levobupivacaine 0.5% and diluted with 1 ml 0.9 NaCl to make a total volume. Then, continuous infusion was used as 5 ml/hr of the specific mixture of each group till the end of the surgery. This trial was so planned that neither the doctor nor the patients were aware of the groups and the drug used. Patients of either sex, age group of 20 to 60 years with ASA grade I & II, undergoing lower abdominal and pelvic surgeries with duration of surgery (1-2 hrs) were included. Patient having contraindications for epidural anaesthesia (infection at the site of injection, spine deformity, coagulopathy disorders, patient receiving anti-platelet drugs such as aspirin,

clopidogrel, patient receiving heparin, pre-existing neurological defects), Known hepatic, renal, cardiac, neurological, psychiatric, metabolic or respiratory disease, Evidence of gross radiological and anatomical abnormality in lumbar region, Patient refusal were excluded from study. Pre-anaesthetic check-up was done a day before surgery which includes complete history of patient local examination of lumbo-sacral region to look for presence of any deformity, general physical and systemic examination, routine investigations were done. Patient was kept fasting for 8 hours pre-operatively. After epidural block, the onset of sensory block was defined as the time from the epidural injection of the study drug to the time taken to achieve the sensory block up to T10 dermatome level. This was assessed by pin prick test bilaterally in mid-clavicular line by using 25G hypodermic needle. Onset of motor block was defined as the time from epidural injection of the study drug to the time taken to achieve motor block by using modified Bromage scale 3. Total duration of Analgesia was time from epidural drug administration to patient's first demand of rescue analgesia. (On VAS 3). The side effects were noted and managed accordingly.

**Visual analogue score:** Postoperatively, the pain was assessed by using visual analogue pain scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain).



The collected data was entered in Microsoft Excel and then was analysed and statistically evaluated using SPSS-PC-17 version. Quantitative data was expressed by mean, standard deviation and difference between comparable groups were tested by student's t-test (unpaired) or Mann Whitney 'U' test, while qualitative data was expressed in percentage. Difference between the proportions were tested by chi square test or Fisher's exact test. 'P' value less than 0.05 was considered statistically significant.

#### Results:

The patients ranged from 20 years to 60 years of age with mean age of Group A  $38.20 \pm 2.44$  years and Group B was  $37.47 \pm 2.62$  year. Distribution of sex was similar in both groups, mean weight and height in the two groups is almost same and statistical comparison between the mean weight and height is non-significant. ASA grade distribution between two groups is non-significant. Comparison of mean heart rate, mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure and SPO2 in two groups at different time intervals which showed that they were statistically non-significant.

**Table 1: Socio Demographic Profile**

	Group A		Group B		P value
AGE GROUP	No.	%	No.	%	
42-50	17	56.67	19	63.33	0.266
51-59	13	43.33	11	36.67	
Mean ± SD	38.20±2.44		37.47±2.62		
SEX					
Male	12	40.00	13	43.33	1.00
Female	18	60.00	17	56.66	
HEIGHT & W EIGHT					
	Mean	SD	Mean	SD	
Weight	67.57	10.554	68.70	9.34	0.661 (NS)
Height	161.50	6.74	161.23	7.07	0.881 (NS)
ASA GRADE					
Grade 1	23	76.66	24	80.00	0.584
Grade 2	7	23.33	6	20.00	
DURATION OF SURGERY					
	Mean	SD	Mean	SD	
Mean duration	108.83	4.36	108.47	5.44	0.814
Median	109.50		109.00		

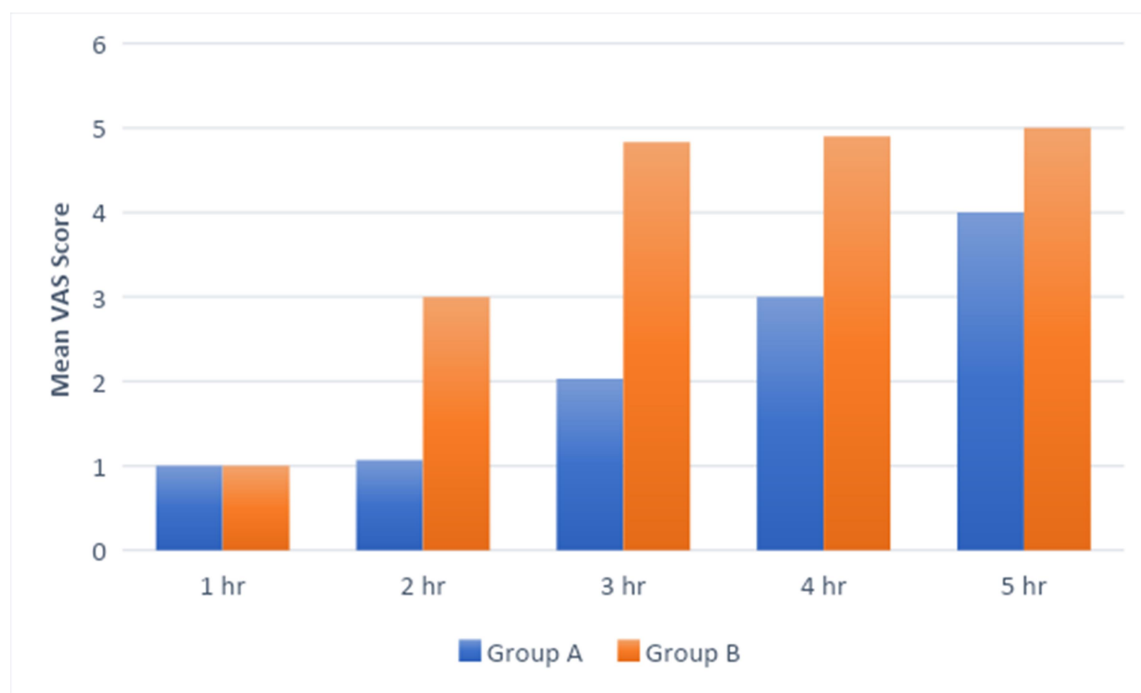
**Table 2**

Mean time of onset sensory block (11.70 $\pm$ 1.06 min) and motor block (15.57 $\pm$ 1.55 min) was less in Group A than Group B and statistical comparison between onset of sensory and motor block is significant. Time to first analgesic requirement is lower in group (B) as compared to group (A) and statistically significant. The time required for rescue analgesia was less in Group B than with Group A, which means Group A has longer action for relief of pain.

	Group A		Group B		Result (p value)
	Mean	SD	Mean	SD	
<b>Sensory Block</b>	<b>11.70</b>	<b>1.06</b>	<b>17.50</b>	<b>0.86</b>	<b>p&lt;0.001 (S)</b>
<b>Motor Block</b>	<b>15.57</b>	<b>1.55</b>	<b>22.70</b>	<b>1.29</b>	<b>p&lt;0.001 (S)</b>
<b>Analgesic requirement (in min)</b>					
<b>Mean time</b>	<b>287.40</b>	<b>9.00</b>	<b>157.50</b>	<b>8.17</b>	<b>p&lt;0.001 (S)</b>

Fig. 1 Comparison of post operative VAS score in two groups

shows that there is a statistically significant difference in VAS score in group A and group B for 2 hr, 3 hr 4 hr and 5 hr and VAS score is higher in group B as compare to group A.



**Table 3:** Complications

	Group A (n=30)		Group B (n=30)	
	No.	%	No.	%
Nausea	3	10.00	4	13.33
Vomiting	0	0.00	0	0.00
Pruritus	0	0.00	0	0.00

In Group A 10 % patients had nausea and Group B 13.33% patients. There was no significant difference between the two groups with regard to these side effects. There was no bradycardia, hypotension and respiratory depression in any of the group.

## DISCUSSION

Regional anaesthesia is now more popular than general anaesthesia for infraumbilical and pelvic surgeries because of the increased mortality rate associated with general anaesthesia. Excessive high regional blocks and local anaesthetics toxicity are the commonest causes of mortality associated with regional blocks. Epidural anaesthesia, nowadays a widely practiced regional anaesthesia technique in lower abdominal and pelvic surgeries. Beneficial effects of epidural anaesthesia over spinal anaesthesia are decreased frequency of hypotension, extended duration of

surgery and effective postoperative analgesia, allowing the patient to be pain free at rest and when mobilizing. It also reduces the surgical stress response, mortality and morbidity after surgery. The local anaesthetic drugs currently available for epidural anaesthesia offer a varied degree of efficacy, from drugs of low potency such as procaine to drugs eight to ten times potent such as bupivacaine and etidocaine.

Unfortunately, as the potency of local anaesthetics increases so does their toxicity. Bupivacaine, one of the most widely utilized local anaesthetics has been the subject of intense investigation because of sudden cardiovascular collapse in some patients. Levobupivacaine (S-1-butyl-2-piperidylformo-2',6'-xylidide hydrochloride), the pure S(-)-enantiomer of racemic bupivacaine, is a new long-acting local anesthetic that has recently been introduced in the clinical routine. Because of its significantly decreased cardiovascular and central nervous system toxicity, levobupivacaine seems to be an attractive alternative to bupivacaine.<sup>7</sup>

Magnesium sulphate is a good agent as an adjuvant in epidural anaesthesia as it noncompetitively blocks NMDA (N-Methyl-D-Aspartate) receptors, thus prevent the activation of this in the dorsal horn of spinal cord by the excitatory neurotransmitter (like aspartate and glutamate) released from the peripheral nociceptive stimulus. Central sensitization plays the key role in development of chronic pain which is blocked by magnesium by inhibiting the NMDA receptors.<sup>8</sup>

Our study was done to evaluate the post-operative analgesic effect of Magnesium sulphate added to levobupivacaine in epidural anaesthesia for lower abdominal and pelvic surgeries. In the present study, a total of 60 patients were randomly allocated into two groups, Group A (MgSO<sub>4</sub> and Levobupivacaine Group) and Group B (Levobupivacaine Group) consisting of 30 patients each by using sealed envelope method. In our study, We compared Onset of Sensory and Motor block, VAS score, Time of first rescue analgesia, Hemodynamic variables and any complication occurred in both groups.

#### **Demographic Variables:**

Both groups were almost similar for age, sex, physical parameters and duration of surgery. Mean age in group A and B were 38.20±2.44, 37.47±2.62 respectively for two groups. Distribution of sex was similar in both groups with 60.00 % females and 40.00 % males in the Group A, 56.66% females and 43.33 males in Group B and M:F ratio in two groups was 12:18, 13:17 in groups A and B respectively. Mean height and weight, ASA grades and duration of surgery in the two groups were statistically insignificant.

#### **Onset of sensory and motor block:**

In our study, the mean time of onset sensory block 11.70±1.06 min in Group A and 17.50±0.86 min in Group B and mean time of onset of motor block 15.57±1.55 min in Group A and 22.70±1.29 min in Group B and statistical comparison between onset of sensory and motor block is significant (P<0.05). In this study, the addition of MgSO<sub>4</sub> significantly enhanced the onset of sensory and motor block. Our results were similar **Ghatak et al.**<sup>9</sup> who found that the addition of magnesium as an epidural anaesthetic adjuvant in lower abdominal and lower limb surgeries. The muscle relaxant effect of MgSO<sub>4</sub> is due to the calcium channel blocker MgSO<sub>4</sub> prevents the passive release of calcium by the sarcoplasmic reticulum and induces muscle relaxation. Also, it affects neuromuscular transmission as

it reduces the presynaptic release of acetylcholine (ACH); the decreased ACH level will affect the postsynaptic muscle receptors and increase the threshold of axonal excitation.<sup>9</sup>

The reported beneficial effects of adding magnesium to local anaesthetic for postoperative analgesia could be attributed to the more analgesic effect of magnesium sulfate during the phase 2 of pain mechanism<sup>8</sup>, to attenuation of spinal release of amino acids acting as agonists for NMDARs, or to direct block of NMDA glutamate channel.<sup>10</sup> However, a supposed local analgesic effect of magnesium was proposed depending on the findings recorded by **Narang et al.**<sup>11</sup> who found that magnesium sulfate when added as an adjuvant to lignocaine during intravenous regional anaesthesia fastens the onset of sensory and motor block and decreases tourniquet pain.

#### **VAS Score:**

In Our study there was a significant difference in VAS score in group A and group B for 2 hr, 3 hr, 4 hr, 5 hr. VAS score was higher in group B as compare to group A. This clinical study demonstrated that the epidural MgSO<sub>4</sub> had a potent analgesic effect as it prolongs the postoperative pain-free period and first request of analgesia with a significant reduction in analgesic requirements. Moreover, it is a good adjuvant to levobupivacaine as it fastens the sensory and motor block with better abdominal relaxation. The predominant analgesic effect of epidural magnesium is attributed to its non-competitive antagonist to NMDA receptor which is ligand-gated ion channels that generate slow excitatory postsynaptic currents at glutamatergic synapses. The sustained activation of NMDA receptor promotes intracellular signalling that culminates in long-term synaptic plasticity, wind up phenomenon, and central sensitization. In addition, the antagonist of NMDA receptor prevents the hyperalgesia, allodynia, and the induction of central sensitization.<sup>8</sup> The analgesic effect of magnesium was evident by significant reduction of postoperative analgesic consumption which is in accordance with **Bilir et al.**<sup>2</sup> Similar analgesic effects of magnesium were reported by **Yousef and Amr**<sup>8</sup> who obtained approximately 153 min prolongation of the duration of postoperative analgesia by addition of 500 mg MgSO<sub>4</sub> to epidural bupivacaine and fentanyl. **Malleeswaran et al.**<sup>12</sup> also obtained approximately 42 min prolongation of the duration of spinal anaesthesia by addition of 50 mg MgSO<sub>4</sub> to the intrathecal combination of bupivacaine and fentanyl. **Ghatak et al.**<sup>13</sup> also compared magnesium sulfate or clonidine along with epidural bupivacaine for surgical anaesthesia in patients undergoing lower abdominal and lower limb surgeries and reported that magnesium sulfate is a predictable and safe adjunct to epidural bupivacaine for rapid onset of anaesthesia, whereas clonidine provided prolonged duration of anaesthesia with sedation.

#### **Time Of Rescue Analgesia:**

In the present study, the mean time to first analgesic requirement was lower in group (B) as compared to group (A) and statistically significant. The time required for rescue analgesia was less in Group B than with Group A, which means Group A has longer action for relief of pain. There are very few studies that examined the effect of adding MgSO<sub>4</sub> to epidural levobupivacaine on postoperative analgesia. Moreover, most of the studies that evaluated the postoperative analgesic effect of epidural MgSO<sub>4</sub> used a single dose of epidural Mg, either added preoperatively or postoperatively. However, pre- plus continuous intraoperative epidural MgSO<sub>4</sub> infusion was examined by few studies. **Arcioni et al.**<sup>14</sup> in their study concluded that, supplementation of spinal anaesthesia with combined subarachnoid and epidural MgSO<sub>4</sub> in patients undergoing orthopedic surgery significantly reduced postoperative analgesic required by the patients after major orthopedic surgeries without affecting hemodynamics. **Kandil et al.**<sup>15</sup>



also found in their study that the preemptive use of epidural MgSO<sub>4</sub> to reduce narcotic requirements in orthopedic surgery. They found that adding magnesium to epidural bupivacaine is associated with significant improvement in VAS and significant reduction in the number of patients requesting early postoperative analgesia as well as total fentanyl consumption. **Hasanein et al.**<sup>16</sup> in their study concluded that the effect of single dose of 50 mg epidural Mg as an adjuvant to bupivacaine 0.125% and 50 µg fentanyl for labor analgesia. It was associated with faster onset, longer duration of action, and reduced the breakthrough pain with no side effects on mother and fetus assessed by Apgar score, cord blood acid-base status, and fetal HR tracings. On sixty patients undergoing hip replacement surgeries using combined spinal–epidural anaesthesia. **Kayalvizhi et al.**<sup>17</sup> found in their study that the postoperative analgesic effect of single dose 50 mg MgSO<sub>4</sub> added to epidural fentanyl 50 µg at the end of the surgery in comparison to epidural fentanyl 50 µg only. They found that it was associated with more prolonged analgesia and less rescue analgesic requirements than that found with epidural fentanyl only.

In agreement with the current study, **Farouk**<sup>8</sup> evaluated the preemptive analgesic effect of Mg when added to a multimodal patient-controlled epidural analgesia (PCEA) on ninety patients scheduled for abdominal hysterectomy under general anaesthesia, who were allocated into one of three groups. (1) Pre-Mg group received a bolus of epidural Mg 50 mg before induction of anaesthesia, then infusion of 10 mg/h till the end of surgery. (2) Post-Mg group received epidural saline during the same time periods and bolus epidural Mg 50 mg at the end of surgery. (3) Control group received epidural saline during all three periods. Immediately postoperatively and continued for 3 days, patients in the two Mg groups received PCEA with fentanyl 1 µg/ml, bupivacaine 0.08%, and Mg 1 mg/ml, and patients in the control group received PCEA with fentanyl 1 µg/ml and bupivacaine 0.08%. Lower pain scores and lower analgesic consumption were recorded in the pre-Mg group compared to the post-Mg and control groups, and in the post-Mg group compared to the control group, with no detected sides effects. **El-Kerdawy**<sup>18</sup> also found in their study that, for lower extremity orthopedic procedure, supplementation of spinal anaesthesia with combined intrathecally injected and epidurally infused Mg considerably reduced the perioperative analgesic requirements without any side effects.

#### **Hemodynamic Parameters:**

In our study there was no clinically significant hemodynamic changes in both the groups. In agreement with the current study, **Bilir et al**<sup>2</sup> in their study of epidural Magnesium and Fentanyl for postoperative pain, found that SBP, DBP, MAP, pulse rate and oxygen saturations remained stable and there was no significant difference between the groups.

#### **Complications:**

In our study no significant side effects were observed in the form of vomiting, and respiratory depression. In Group A 10 % patients and in Group B 13.33% patients had nausea. There was no significant difference between the two groups with regard to these side effects. Our results coincides with **Nethra SS et al.**<sup>19</sup> who compared bupivacaine alone and with MgSO<sub>4</sub> for epidural anaesthesia in infraumbilical surgeries and reported that the frequency of side effects were similar between the two groups.



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