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Comparison between adenosine and magnesium sulfate as an adjuvant for ultrasound-guided rectus sheath block. A prospective randomized controlled study

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ABSTRACT

Background: Rectus sheath block (RSB) is an effective nerve block. This study aimed to compare adenosine and magnesium sulfate as an adjuvant for ultrasound-guided RSB (UG-RSB).

Methods: This prospective controlled randomized trial was performed on 96 adult patients (ASA I and II) undergoing umbilical or epigastric hernia repair. The patients were assigned randomly to three equal groups and got bilateral UG-RSB. Adenosine group: using 20 ml bupivacaine hydrochloride 0.25% + 12 mg of adenosine (4 ml) +1 ml saline 0.9%. Magnesium group: using 20 ml bupivacaine hydrochloride 0.25% + 500 mg of magnesium sulfate (5 ml). Control group: using 20 ml bupivacaine hydrochloride 0.25% + 5 ml of saline 0.9%. Registration No.: 6/2018ANET17

Results: A significant postoperative reduction of VAS up to 18 h was detected in the magnesium sulfate group and up to 12 h was detected in the adenosine group. A statistically significant prolongation of time to the first analgesia in magnesium and adenosine groups than control groups ($483.44 \pm 48.03 \& 415.28 \pm 29.81$ than 325.31 ± 50.29 , respectively), as well as the mean postoperative morphine consumption was 5.94 ± 1.61 , 8.03 ± 1.0 and 16.69 ± 2.49 among magnesium, adenosine, and control groups, respectively. The postoperative complications were statistically significantly higher in the control group.

Conclusion: This study validates the effectiveness of adenosine versus magnesium sulfate as good adjuvants for improving the quality and duration of UG-RSB and reduction of post-operative narcotic requirements. However, the duration was relatively longer with magnesium sulfate.

1. Introduction

Postoperative pain management is annoying for patients with midline abdominal operations as severe pain is associated with insomnia, delayed mobility, and atelectasis [1]. These factors will result in less patient satisfaction, enhancement of chronic postoperative pain, delayed hospital discharge, and high healthcare costs [2].

Recent multimodal techniques aimed at incisional pain rather than visceral pain, which results in the generation of abdominal field block [3]. Ultrasound (US) guidance offers the advantage of the direct vision of the needle, nervous system, and surrounding structures; as well as more accurate direct delivery of the local anesthetic mixture, which might improve safety and efficacy [4].

Rectus sheath block (RSB) has been described in various surgeries [5]. However, its analgesia is limited to the effect of administered local anesthetic. Thereby,

various adjuncts like opioids, dexamethasone, ketamine, clonidine, dexmedetomidine, ketorolac, and neostigmine have been used to achieve prolonged and dense analgesia [6,7].

Magnesium sulfate is utilized as an adjuvant in peripheral nerve block [8,9]. Analgesic actions of magnesium sulfate are owing to the block of the NMDA receptors and the regulation of calcium influx into the cell. Magnesium sulfate has been also used for hypertension and may prevent postoperative shivering [10].

Adenosine has recently been used systemically, intrathecally, or intraventricularly for analgesia in various pain states [11]. Adenosine compounds provide significant and long-lasting perioperative analgesia through central A1 receptor-mediated antinociceptive actions as well as via peripheral A2a or A3 receptor-mediated anti-inflammatory actions [12].

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This study aimed to compare the efficiency of adenosine to magnesium sulfate as adjuvants for ultrasound-guided rectus sheath block (UG-RSB).

1.1. Ethical approval

The study was performed after IRB permission (6/ 2018ANET17) from the Local Research and Ethical Committee, Faculty of Medicine Menoufia University. All the patients provided informed written acceptance.

2. Patient and methodology

A prospective randomized controlled trial was conducted in Menoufia University Hospitals between June 2019 and January 2021. Ninety-six adult patients aged 18–60 years old of both genders, of ASA I and II class, who were scheduled for undergoing umbilical or epigastric hernia repair under general anesthesia (GA) were randomly assigned into three groups (32 patients each) by closed envelope technique. The assessors and patients were blinded to the adjuvants of our study. The local anesthetic solution for all groups was prepared and coded by a distinct anesthesiologist not included in patient follow-up.

2.1. Adenosine group

This group received bilateral UG-RSB using 12 mg of adenosine (4 ml) and 1 ml saline 0.9% added to 20 ml bupivacaine hydrochloride 0.25% (total volume 25 ml on each side).

2.2. Magnesium group

This group received bilateral UG-RSB using 500 mg of magnesium sulfate (5 ml) added to 20 ml bupivacaine hydrochloride 0.25% (total volume 25 ml on each side).

2.3. Control group

This group received bilateral UG-RSB using 20 ml bupivacaine hydrochloride 0.25% and 5 ml of saline 0.9% (total volume 25 ml on each side).

Patients were excluded if they refused to participate, complained of coagulopathy or allergy to bupivacaine or other study drugs, were morbidly obese (body mass index more than 35 kg/m²), or had a local infection at the injection site.

Preoperative assessment of the patients was done by a detailed history, clinical examinations, and basic investigations such as CBC, sGPT, sGOT, urea, creatine, and coagulation profile.

Continuous pulse oximetry, electrocardiography, non-invasive arterial blood pressure, and capnography were applied during the perioperative period. Premedication with i.v (intravenous.) ranitidine 50 mg, midazolam (0.03 mg/kg), and prophylactic antibiotic were given.

General anesthesia was carried out with fentanyl 1.3 μ g/kg, propofol 1.5 mg/kg, and rocuronium 0.5 mg/kg to facilitate tracheal intubation. Isoflurane (1–1.2%) was used to maintain anesthesia. I.V. fentanyl bolus 1 μ g/kg was titrated to keep the BP and HR within 20% of baseline levels. The patients were mechanically ventilated targeting EtCO₂ of 35–40 mmHg on O₂/air mixture (1:1).

After induction of GA, while the patient was lying supine, the ultrasound probe was positioned at the umbilical level, and then bilateral single-injection UG-RSB was carried out on all patients using a 38 mm broadband linear array ultrasound probe (5–10 MHz). The needle was positioned in the plane and then advanced under direct ultrasound visualization through the body of the rectus muscle till it attained the plane between the rectus muscle and posterior rectus sheath. After negative aspiration was ensured, the study solutions were injected which led to the expansion of this potential space.

After extubation and complete recovery, all patients were transferred to the post-anesthesia care unit (PACU) till being sure of hemodynamic stability and had no pain, nausea, or vomiting before discharge to the ward. The total intraoperative fentanyl, surgery time, anesthesia time, and PACU stay were recorded. In the PACU, the hemodynamic measurements, VAS on movement, and Ramsay sedation score (RSS) were recorded on arrival and every 15 min, therefore, they were recorded immediately, 1, 2, 3, 6, 12, 18, and 24 h in the ward to assess possible postoperative sedative effects of the used local anesthetic adjuvants or narcotics.

Postoperative analgesia was given as i.v. infusion of 15 mg/kg paracetamol every 8 h and i.v. increments of 2 mg morphine till the VAS score became <3 cm with a timeout of 20 min. I.V. ondansetron 4 mg to manage reported nausea and/or vomiting. The time to the first analgesic, total number of rescue analgesia and ondansetron, and total amounts of postoperative analgesics were recorded for 24 h. RSS grades were defined as 1 means a patient is anxious and fully awake, 2 means a patient is fully awake, 3 means a patient is conscious but drowsy, 4 means a patient is asleep but reactive to verbal commands, 5 means a patient is asleep but responsive to palpable stimulus, and 6 means a patient is asleep and not responsive to any stimulus [13].

Postoperative troubles such as nausea and vomiting, somnolence, shivering, pruritus, and respiratory depression were recorded.

2.3.1. Statistical analysis

The primary outcome was the time to the first postoperative morphine request (VAS score \geq 3) from the completion of the local anesthetic injection. Based on Ammar et al. [14], who compared adenosine and magnesium sulfate addition to local anesthetic for transversus abdominis plane block, showing an effect size for analgesia duration to be 0.69, the sample size was calculated at $\beta = 0.10$ and $\alpha = 0.05$, and it was estimated to be 30 patients per each group. Accounting for a dropout of 5%, a total of 32 patients per group were included in the study.

SPSS 21 software (SPSS Inc. USA) was used to analyze the data. Quantitative data were represented as mean \pm (SD) standard deviation, and ANOVA (analysis of variance) was used for comparison. This was followed by post hoc tests (LSD) if there was a statistical difference between the groups. Pain scores were represented as median (Min.-Max.) and analyzed by the Kruskal – Wallis H test. If a statistical difference was detected, the comparison between groups was conducted by using post hoc tests (Mann-Whitney U test). The chi-square χ 2 test was used to compare two or more qualitative groups in the categorical data. *P* values less than 0.05 were considered statistically significant.

3. Results

A total of 101 entrants were enrolled in our study. Five of them did not match the inclusion criteria, three patients denied collaborating, one patient had a bleeding tendency, and one patient had a history of drug allergic reaction, and 96 were included and randomized, and their data were analyzed (Figure 1).

The collected demographic data, surgery time, and anesthesia time revealed non-significant variations between the three groups (P > 0.05), indicating good matching (Table 1).

A non-significant variation was observed between the three studied groups at different time points regarding intraoperative hemodynamic measurements up to 3 h postoperatively; after that, still, there was no statistically significant difference between adenosine and magnesium groups up to 24 h while, there was statistically significantly increase in the control group (postoperative 6th h and 12th h) to be comparable again after 18 h postoperatively (Figures 2,3)

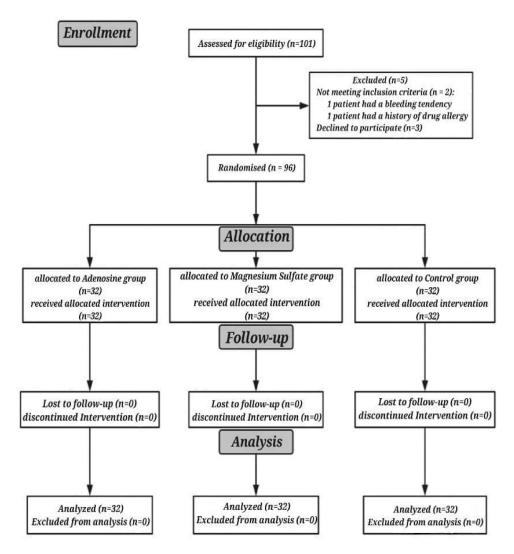


Figure 1. Consolidated standards of reporting trials (CONSORT) flow diagram.

Table 1. Comparison of the demographic and surgical characteristics of the patients.

	2 1 2				
	Adenosine $(n = 32)$	Mg (<i>n</i> = 32)	Control (<i>n</i> = 32)	Test of Sig.	р
Age (Years)	40.03±7.92	41.13±8.55	38.53±5.96	F=0.950	0.391
Sex (M/F)	22/10	21/11	22/10	$\chi^2 = 0.095$	0.953
Weight (Kg)	75.84±4.44	75.19±3.86	76.19±5.90	F=0.356	0.701
Height (Cm)	170.44±8.35	168.34±7.50	169.53±7.37	F=0.587	0.558
$BMI (kg/m^2)$	26.24±2.51	26.62±2.03	26.51±1.50	F=0.294	0.746
ASA (I/II)	18/14	17/15	16/16	$\chi^2 = 0.251$	0.882
Surgery time (min)	78.94±7.03	81.13±6.55	80.0±7.01	F=0.811	0.447
Anesthesia time (min)	93.53± 7.50	95.84± 6.58	94.75± 7.18	F=0.850	0.431
Fentanyl consumption (µg)	174.25± 10.16	173.00 ± 8.82	175.22 ± 13.48	F=0.328	0.722
PACU stay (min)	51.41±7.21	52.66±7.40	53.44±6.65	F=0.667	0.516

Data were expressed in mean \pm SD.F: F for One way ANOVA χ^2 : Chi-square test.

P: p-value for comparing between the three studied groups *: Statistically significant at $p \le 0.05$

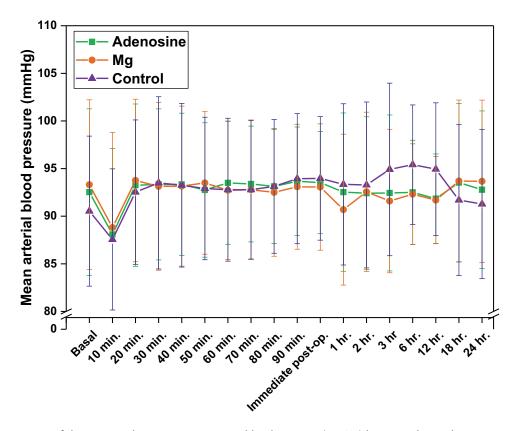


Figure 2. Comparison of the intra- and post-operative mean blood pressure (mmHg) between the study groups.

A non-statistically significant variation was observed between the three studied groups regarding intraoperative fentanyl consumption or PACU stay (Table 1).

A statistically significant elongated analgesic duration was observed in the magnesium group (483.44 ± 48.03) compared to the adenosine group (415.28 ± 29.81) ; however, it was significantly lower in the control group (325.31 ± 50.29) than both (Table 2).

The total postoperative morphine consumption and the frequency of rescue analgesia were statistically significantly lower in the magnesium group compared to the adenosine group, furthermore, both were significantly lower than in the control group (Table 2).

A non-significant difference was observed between the three studied groups regarding VAS for the first three postoperative hours. However, in the 6th and 12th hours postoperatively, the VAS scale was increased significantly in the control group, with non-significant variation between the adenosine and magnesium groups, as the median of the VAS scale in 6th hours in the control group (= 4.5) as compared to adenosine (= 2.5) and magnesium groups (= 2.25); while the median scale in 12th hours in the control group (= 4) as compared to adenosine (= 3) and magnesium groups (= 2.5).

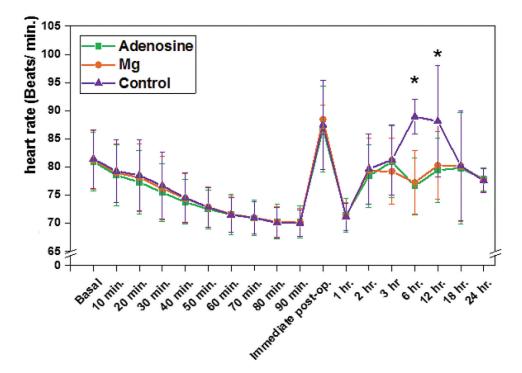


Figure 3. Comparison of the intra- and post-operative heart rate (Beats/min.) between the study groups.

Table 2. Comparison of th	e postoperative	characteristics	between the study groups.

	Adenosine $(n = 32)$	Mg (<i>n</i> = 32)	Control $(n = 32)$	Test of Sig.	р
Duration of analgesia (min.)	415.28±29.81 ^b	483.44±48.03 ^c	325.31±50.29 ^a	F=105.49	<0.001
Sig. bet. grps		p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*			
Postoperative paracetamol (mg)	2197.5± 915.80 ^b	1987.0±523.3 ^c	3434.5±269.0 ^a	F=49.55	<0.001
Sig. bet. grps		p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*			
Postoperative morphine consumption (mg)	8.03±1.00 ^b	5.94±1.61 ^c	16.69±2.49 ^a	F=318.25	<0.001
Sig. bet. grps		p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*			
Rescue analgesia	6 (4–9)	3 (2–5)	9 (8–12)	H=48.21	<0.001
Sig. bet. grps		p ₁ <0.001**, p ₂ <0.001**, p ₃ <0.001**			
VAS 0 h	0.5 (0-1)	0.5 (0–1)	1 (0-2)	H=3.953	0.139
1 h	1.5 (0-2)	1.5 (0–2)	1.5 (1–3)	H=3.841	0.147
2 h	1 (0.5–2.5)	1 (0–2)	1.75 (0–3.5)	H=4.062	0.131
3 h	2 (1-4)	2.5 (0–3)	3 (2-4.5)	H=5.962	0.051
6 h	2.5 ^b (2–3)	2.25 ^b (1–3)	4.5 ^a (4–5)	H=66.642	<0.001
Sig. bet. grps		p ₁ =0.077, p ₂ <0.001**, p ₃ <0.001**			
12 h	3 ^b (2–4)	2.5 ^b (1–3)	4 ^a (4–5)	H=63.271	<0.001
Sig. bet. grps		p ₁ =0.189, p ₂ <0.001**, p ₃ <0.001**			
18 h	4 ^b (3–4.5)	2.5 ^a (2–3)	4 ^b (4–5)	H=64.306	<0.001
Sig. bet. grps		p ₁ <0.001**, p2 =0.076, p ₃ <0.001**			
24 h	4 (3.5–4)	4 (3-4.5)	4.25 (3-5)	H=4.413	0.110
No of pt. need Ondansetron No. (%)	5 (15.6%)	2 (6.3%)	14 (43.8%)	χ ² =14.263	0.001
Sig. bet. grps		^{FE} p ₁ =0.426, p ₂ <0.05*, p ₃ <0.001*			

Data were expressed by using mean \pm SD for normally distributed quantitative variables, Qualitative data were described using median (Min. - Max.). F: F for One way ANOVA, *: LSD for multiple comparisons test.

H: H for Kruskal Wallis test, **: Mann-Whitney U test for multiple comparisons test.

x²: Chi-square test, FE: Fisher Exact for multiple comparisons test.

p1: compare Adenosine group and Magnesium group.

p_{2:} compare Adenosine group and control group.

p3: compare Magnesium group and control group.

VAS and Rescue analgesia were expressed as median and (min-max).

Common letters are non-significant (i.e., Different letters are significant).

In 18^{th} hours postoperatively, the VAS scale was significantly lower in the magnesium group (median = 2.5) (p1 < 0.001 & p3 < 0.001) compared to the adenosine and control groups (median = 4 in both)

However, after 24 h, there was no statistical variation in the VAS scale among the three groups (P = 0.110). The median = 4 in the adenosine and magnesium groups and 4.25 in the control group (Table 2). The patients who needed postoperative ondansetron were significantly more frequent in the control group (43.8%) than in the adenosine and magnesium groups with non-significant variation between the adenosine group (6.3%) and the magnesium group (15.6%) (Table 2).

As regards the postoperative sedation score, there was no statistically significant variation between

Table 3. Comparison of post-operative Ramsay sedation score (RSS) between the study groups.

	Adenosine $(n = 32)$	Mg (n = 32)	Control $(n = 32)$	Test of Sig.	р
0.0 H	4 ^b (1–5)	4 ^b (2–5)	4.5 ^a (3–6)	H=11.759	<0.05
(Time of PACU admission)					
1.0 H	3 ^b (1–4)	3 ^b (1–4)	4 ^a (1–4)	H=11.319	< 0.05
2.0 H	2 ^b (1–3)	2 ^b (1–4)	3.5 ^a (2–4)	H=42.724	< 0.001
3.0 H	2 (1-3)	2 (1-3)	2(1-3)	H=1.307	0.520
6.0 H	1 (1–2)	1 (1-2)	1 (1–3)	H=4.980	0.083
12.0 H	1 (1–2)	1 (1-2)	1 (1–2)	H=3.167	0.205
18.0 H	1 (1–2)	1 (1-2)	1 (1–2)	H=1.080	0.583
24.0 H	1 (1–2)	1 (1–2)	1 (1–2)	H=0.270	0.874

RSS was expressed as median and range p was calculated using Kruskal–Waills test (H: H for Kruskal–Wallis test). Common letters are not significant (i.e., Different letters are significant). Using Mann-Whitney U test.

p: p-value for comparing the three studied groups Statistically significant at $p \le 0.05$.

adenosine and magnesium groups at all measuring times. While it was statistically significantly higher in the control group during the first two postoperative hours with no difference among the three groups after that (Table 3).

As regards the postoperative sedation score, there was no statistical significant variation between adenosine and magnesium groups at all measuring times. It was statistically significantly higher in control group during the first two postoperative hours with no difference among the three groups after that (Table 3).

PONV was statistically significantly less in the magnesium group (6.3%) and in the adenosine group (15.6%) compared to that of the control group (43.8%) (p <0.001), with no difference between the magnesium and adenosine groups. The somnolence was statistically significantly higher among the control group (31.3%) compared to the adenosine and the magnesium groups (6.3%, each) with a statistically significant variation, with no variation between magnesium and adenosine groups. The other postoperative complaints were highly observed among the control group; shivering (12.5%), pruritus (3.1%), and respiratory distress (6.3%) as compared to the adenosine group (6.3%, 3.1%, and 0.0%, respectively) and magnesium group (3.1%, 0.0%, and 3.1%, respectively). However, these differences were not statistically significant (Figure 4).

4. Discussion

The anterior forks of the T_7-T_{11} spinal nerve supply the central part of the anterior abdominal wall; these branches fall between the posterior rectus sheath and the rectus abdominis muscle [15]. As the tendinous cross-roads of the rectus muscle are not adhered to the posterior rectus sheath; LAs can spread cephalocaudally within this potential space and help control postoperative pain [16].

The present study demonstrated that magnesium sulfate and adenosine as adjuvants for bilateral UG-RSB were effective in improving the duration and the intensity of the postoperative analgesia, which were reflected by less postoperative opioid rescue and consumption as well as proper hemodynamic stability. Magnesium sulfate more effectively prolongs the duration of the block than adenosine, as well as it was associated with lower pain scores up to 18 h. The decreased analgesic duration of adenosine may be due to its fast metabolism [17].

We observed that magnesium sulfate and adenosine were associated with fewer postoperative side effects than the control group, despite bilateral block, most probably due to minimal systemic absorption of these doses of adjuvants in addition to proper postoperative analgesia with fewer postoperative opioid requests with their

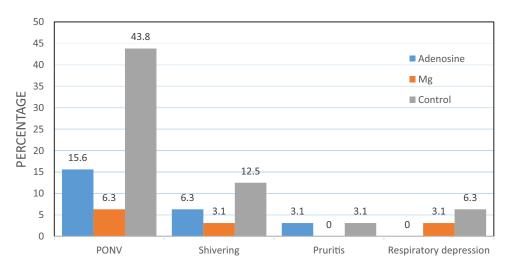


Figure 4. Comparison of the postoperative complications between the study groups.

adverse effects like excessive sedation, respiratory depression, and postoperative nausea and vomiting that also reflected by less ondansetron consumption in our study.

This came in agreement with, Gurbani [11] who compared infra-clavicular block by bupivacaine 0.5% with 75 mg magnesium sulfate versus 6 mg adenosine as a bolus followed by infusion at a rate of 5 ml/h for upper limb surgeries. The author concluded that magnesium sulfate gave prolonged and better analgesia than adenosine. However, adenosine resulted in rapid onset and recovery of motor and sensory blocks.

Ibrahim and Sultan [18] agreed with the present study, they found the patients who received 500 mg magnesium sulfate or 12 mg adenosine as an adjuvant to 0.25% bupivacaine in pectoral nerve block for modified radical mastectomy had a longer block duration and decreased postoperative morphine uses compared to the bupivacaine only group. Moreover, the analgesia was in favor of magnesium rather than the adenosine group.

Mahmoud and Ammar [19] studied adenosine as an adjuvant to local anesthetics in the brachial plexus block. The authors preferred adding adenosine to increase the block duration and minimize postoperative analgesic consumption. Moreover, they advised more research to validate the role of adenosine in local nerve blocks. This came in line with the present study. But we also compared the effect of magnesium sulfate and found its better results than adenosine when added to the local anesthetic.

Also, Dogru et al. [20] added magnesium to levobupivacaine in the axillary brachial plexus block for arteriovenous fistula surgery. Also, Lee [21] examined adding magnesium sulfate to bupivacaine in an interscalene block. They deduced that magnesium sulfate elongated the block duration and minimized postoperative pain.

In agreement with the present study, Al-Refaey et al. [22] examined magnesium sulfate as an adjuvant to bupivacaine for (TAP) transversus abdominis plane block for laparoscopic cholecystectomy and found prolonged postoperative analgesia and decreased analgesic requirement, nausea, and vomiting.

Gunduz A. et al. [8] elaborated on the use of magnesium added to prilocaine for axillary plexus block. Our findings supported them in the elongated block duration and lesser doses of analgesics consumption.

The present study supported Ekmeckzi et al. [9] who studied femoral nerve block for ACL reconstruction, they noticed a prolonged duration of analgesia when adding magnesium to levobupivacaine, however, they reported delayed onset of the block with the usage of magnesium.

Contrary to our findings, Birbicer et al. [23] added 50 mg of magnesium to ropivacaine 0.25% during the caudal block in children, but that failed to provide additional analgesia. This finding may be anatomized by effective pain alleviation with ropivacaine 0.25% alone that may thereby mask the effect of additives, especially

with this small dose in less painful surgery. Furthermore, inaccurate pain evaluation in children by their parents.

Moreover, Choi et al. [24] compared 200 mg of magnesium sulfate to 20 ml ropivacaine 0.2% versus ropivacaine 0.25% alone for brachial plexus block, they did not observe any significant difference regarding postoperative pain intensity, opioid consumption, sedation, and vomiting; this may because they used blinded technique for the block or due to a relatively inadequate magnesium-dose used in their study.

In our study, sedation was statistically more in the control group than in other groups early in the first two postoperative hours, this may be due to the early post-operative morphine requirement for analgesia with its sedative effect. Contrary to our findings, Ibrahim E et al. [18] found delayed sedation in the magnesium and adenosine groups. They attributed this to their antino-ciception effect or delayed absorption from the site of the block. However, we did not detect any delayed sedation; this proves the safety of these adjuvants by this approach.

Our study is a step to improve anesthetic management for special cases. Patients with morbid obesity or obstructive sleep apnea will maximally profit from the addition of adenosine or magnesium sulfate to the bilateral UG-RSB through the opioid-sparing effects [24]. Ischemic cardiac patients or those with stenotic aortic or mitral valve disorders will also profit from proper postoperative analgesia with hemodynamic stability [25]. Also, this technique may be a proportionally safe substitution for a neuraxial block for perioperative pain management in coagulopathic patients [26].

5. Limitation

It should be emphasized that both adenosine and magnesium sulfate may cause bradycardia, vasodilatation, and inhibition of cardiac contractility which may result in hemodynamic adverse effects. Despite the doses of adenosine and magnesium in our study being effective, safe, and without hemodynamic or significant adverse effects, we still need to know where the optimal dose of either adenosine or magnesium may lie, which may give a limitation to the current study.

6. Conclusions

This study validates the effectiveness of adenosine versus magnesium sulfate as good adjuvants for improving the quality and duration of UG-RSB and reduction of postoperative narcotic requirements along with a decrease in postoperative side effects. But the duration was relatively longer with magnesium sulfate.

Acknowledgments

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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