Evaluation of magnesium sulphate in combination with dexmedetomidine as adjuvants to levobupivacaine in ultrasound-guided spermatic cord block: a randomized controlled trial

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Abstract

Background: Several agents have been added to local anesthetics to increase the quality of anesthesia and to prolong postoperative analgesia. The current study investigated the effect of using dexmedetomidine and magnesium sulphate as additives to levobupivacaine 0.5% for spermatic cord block (SCB) anesthesia in testicular sperm extraction (TESE) surgery.

Methodology: It was a prospective, randomized double-blind study, performed on 113 subjects undergoing TESE surgery using local anesthesia. The subjects were randomly divided into four groups. Bilateral SCB was performed for each patient using levobupivacaine 0.5% 18 mL in combination to 2 mL of either normal saline (Group C), dexmedetomidine 1 μg/kg (Group D), magnesium 100 mg (Group M), or a mixture of the same doses of both magnesium and dexmedetomidine (Group MD) according to the group assignment. Patients were compared according to the time of first analgesic dose, and analgesic intake in the first 24 h.

Results: The time elapsed till receiving the first analgesic dose was noted to be longer in the Group MD when compared to those in the Groups C, M and D, (20 ± 1.5 vs 9 ± 1.5, 14.4 ± 2.3 and 15.6 ± 2.2 h, respectively; P < 0.001). Moreover, the requirement of postoperative analgesia was noticeably lower in the Group MD when compared to the other groups.

Conclusion: Using magnesium and dexmedetomidine as additives to levobupivacaine for ultrasound-guided spermatic cord block prolonged postoperative analgesia, and decreased the total postoperative analgesic consumption.

Abbreviations: SCB - spermatic cord block; TESE - testicular sperm extraction; US-SCB - ultrasound-guided SCB

Key words: Dexmedetomidine; Levobupivacaine; Magnesium; Spermatic cord block; Testicular sperm extraction
1. Introduction

One of the most commonly performed procedures for sperm retrieval is testicular extraction (TESE) surgery, which is used to obtain sperm from the epididymis and testes. Despite the use of many different anesthesia techniques for this procedure, the anesthetic technique with the best results for this procedure has always been controversial, as every technique has its pros and cons.1,2

General anesthesia for this operation may help to control the patient anxiety and a more comfortable experience, yet it has an increased prevalence of nausea and vomiting in the postoperative period, which are considered the most common causes of prolonged hospital stay and delayed discharge. The spinal and epidural techniques are considered a risk in cases of cardiac disease or coagulopathy. They may lead to urine retention and hemodynamic instability, which could lead to nausea and vomiting, as well as post-dural puncture headache and backache.3,4

In contrast, local anesthetic (LA) techniques have been proven to be effective means of anesthetizing the testes and epididymis. The nerve supply of the testes and epididymis is derived from both the ilioinguinal and genitofemoral nerves; therefore, injecting a LA agent to the spermatic cord itself can cause anesthesia for both structures. However, the perineal branches of the pudendal nerve that supply the scrotal skin sensation is not anesthetized using this block. Consequently, it has been considered crucial to perform additional LA injection of the skin at the site of incision for optimum results. This block is known as the spermatic cord block (SCB), first described in the 1960s by Earle. Over the past two decades, ultrasound has been introduced to perform the same block under vision. It is considered more perfect, more cost-effective, as well as a safe and effective imaging tool.5-8

Unfortunately, one of the major drawbacks of ultrasound-guided SCB (US-SCB) is a single-injection technique, leading to a short postoperative analgesia duration. To overcome this disadvantage, some adjuvants, including opioids, clonidine, dexamethasone, magnesium, ketamine and α2-adrenoceptors agonists, have been used to prolong the analgesia duration.9

Dexmedetomidine is a powerful selective α2-adrenoceptor agonist, proven to have a LA effect on peripheral nerves by inhibiting release of C-fiber transmitters. It is considered to have less neurotoxic side-effects compared to other agents.10 In contrast, magnesium sulphate is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, as well as a calcium channel blocker. It was used as an adjuvant to LA solution for various types of regional anesthesia and analgesia to enhance the quality and extend the duration of the block.11

We investigated the results of using dexmedetomidine and magnesium sulphate in addition to levobupivacaine 0.5% in US-SCB anesthesia and their effect on the postoperative analgesia in TESE surgery.

2. Methodology

This was a prospective double-blind randomized controlled trial at the Infertility Centre Hospital, after acquiring ethical permission from the Institutional Research Ethics Committee (No. N-19-2020), with registration at www.ClinicalTrials.gov. The objective of the study was fully explained to all participants, including description of the anesthesia procedure that could be used. Moreover, an informed written consent was obtained from all participants involved in this study. We recruited 124 subjects between 20 and 60 y of age, ASA I or II, scheduled for elective TESE under LA. Exclusion criteria included; refusal to participate; ASA III or above, body mass index (BMI) > 40 kg/m², contraindications to LA and allergy to the used medications. The patients who received analgesic medications within the previous 24 h preoperatively were also excluded. Failed block or conversion to general anesthesia (for any cause) were considered a dropout.

Eligible subjects were randomly divided into four groups, based on a computerized randomization number with sealed envelope technique, according to the type of drug/s administered. Randomization and study medication preparation were conducted by an anesthesiologist who had no further involvement in the study. The main agent used in SCB, was 18 mL of levobupivacaine 0.5% (Chirocaine®, Abbott Lab., Italy) in all participants. The additive agents used were:

- Group C: 2 mL of normal saline as placebo,
- Group M: 100 mg of magnesium sulphate 10% in 2 mL,
- Group D: 1 μg/kg dexmedetomidine (Precedex® 100 μg/mL, Hospira, Inc., Lake Forest, IL, USA) in 2 mL, and
- Group MD: mixture of the same doses of both magnesium and dexmedetomidine in 2 mL.

Citation: Wahdan AS, Moussa AA, Farag MA, Salama AK. Evaluation of magnesium sulphate in combination with dexmedetomidine as adjuvants to levobupivacaine in ultrasound-guided spermatic cord block: a randomized controlled trial. Anaesth. pain intensive care 2022;26(2):182-190; DOI: 10.35975/apic.v26i2.1836
The maximum volume injected was 20 mL in all participating subjects.

Two physicians were involved in the study: one experienced in the block technique and one attending physician responsible for data collection. All patients, the surgeon and the investigators were unaware of the patient allocation. Two surgeons performed all surgical procedures using a standard surgical technique. On the day before the surgery, the patients were assessed by taking their medical history, clinical examination and laboratory tests for any of the exclusion criteria mentioned and received briefing about the visual analogue scale (VAS) along with the technique and details of the anesthesia.

On the operative day, the subjects were taken to the preparation area, and shave of the groin area was checked. The demographic data were recorded (age, BMI, ASA, comorbidities and basic VAS); then, a 22G intravenous (IV) cannula was installed, and subjects were given IV bolus of midazolam (0.05 mg/kg) as a premedication and 4 mg of ondansetron and 50 mg of ranitidine IV in 10 min before performing the study. Then, they were taken to the operating room, where standard monitors were attached. The baseline heart rate (HR) and mean arterial blood pressure (MAP) were recorded. All participants received 2–3 L/min supplemental oxygen through nasal prongs. Then, SCB was performed under complete aseptic conditions in the supine position.

2.1. Block technique

Once the inguinoscrotal region was sterilized, the spermatic cord (SC) was palpated at the inguinoscrotal junction and then gently pulled to the surface for better visibility of the anatomical structures and its contents using a 10-MHz linear ultrasound transducer (Siemens ACUSON X300 Ultrasound System) to locate the SC and the cremasteric artery enclosed by the anterior superior iliac spine and pubic tubercle. The SC was defined as a half-circle structure surrounded by fascia. Inside the SC, the Doppler ultrasound was used to recognize the testicular artery, also the vas deferens as a circular non-compressible frame without any Doppler flow signal. After further cleaning of the puncture site and LA infiltration with the same anesthetic mixture, a 22G, 50 mm needle was introduced using an out-of-plane ultrasound technique with the SC located along the short axis and guided to the vas deferens, contralateral to the testicular artery. The tip of the needle was directed forwards to approach the vas. The correct location of the tip of the needle was verified by injecting 0.5–1 mL to examine the expansion of LA around the vas deferens, followed by 10 mL of prepared injectate around it. The same steps were repeated on the opposite side. Each side was anesthetized with 10 mL of the LA mixture and the skin of the scrotum at the site of the incision was injected.

Figure 1: CONSORT flow diagram
using 3–4 mL of the same mixture immediately before surgery. Evaluation of the sensory block onset was done by assessing loss of pinprick sensation. The test was performed every 1 min till loss of sensation to pinprick, and the surgery was started 2 min after. If any additional LA (from the same type of injectate) or analgesics (IV nalbuphine bolus, 100 μg/kg) or sedative (bolus dose of midazolam 0.01–0.03 mg/kg intravenously) had to be given, and/or VAS score was more than 4, or conversion to general anesthesia needed with skin incision, the block was considered unsuccessful. During the intraoperative period, the VAS score, MAP and HR were recorded during the block and then every 15 min throughout the surgery. Complications, such as inadvertent vascular punctures during block, intraoperative cord hematoma and bradycardia or hypotension and nausea and vomiting were noted and managed accordingly. Inj. ephedrine 10 mg was used if MABP fell by 25% from the baseline, atropine 0.6 mg was administered if the HR decreased below 60 beats/min and metoclopramide 10 mg IM for nausea and vomiting.

After the operation, the participants were moved to the post-anesthesia care unit (PACU) for observation and monitoring. Patients were questioned during the first hour in the PACU and later evaluated at every 4 h for 24 h by an independent observer blinded to groups about the intensity of postoperative pain using the VAS. When VAS score was > 4, patients were treated with analgesic protocol, prescribed orally according to the severity of pain as paracetamol + codeine + caffeine (Solpadeine Plus®. Omega Pharma Ltd., UK) one tablet every 6 h, and if the pain was severe (not controlled by paracetamol), ketorolac 10 mg (Ketolac®, Amriya Pharmaceutical Industries, Egypt) two tablets once followed by one tablet every 6 h, under four tablets per day, was prescribed. All patients received omeprazole 20 mg once daily; ondansetron 4 mg orally was prescribed to patients complaining of nausea or vomiting.

The surgeon who performed the surgery was asked to provide scores for the quality of microsurgical conditions using five-point scale (1 = very bad with repeated/vigorous movements and impossible surgery; 2 = bad with many movements/shivering; 3 = good with intermittent abrupt movements; 4 = very good with intermittent slow movements; 5 = excellent without movements).

At discharge time, the patients were given a data sheet to record VAS score and report the time of first analgesic dose and their analgesic consumption and any side effects.

After 24 h of surgery, all patients were contacted by telephone interview to ask them about the recorded data and their opinion about the quality of pain relief using the following scale: 1 = very unsatisfactory; 2 = unsatisfactory; 3 = indifferent; 4 = satisfactory; and 5 = very satisfactory.

The primary outcome was estimated by the time of the first analgesic dose (pain-free time), represented by the time from the block end to the onset of spontaneous testicular pain. While the secondary outcomes were considered the analgesic consumption postoperatively throughout the first day, and success rate of the block, which was defined as painless surgery (VAS) score <4.

### Statistical analysis

The number of participants required for each group was estimated following a power calculation based on data from a previous study. The mean duration of first requirement of analgesia in the levobupivacaine group was 396.13 ± 109.42 min. Based on the assumption that the addition of mixture of study drug to 20 mL.
levobupivacaine 0.5% would prolong the duration for first analgesic requirement by 25%, the least calculated sample size was 27 participants in each group to provide 90% power with a two-tailed significance level at 5% using G*Power 3.1 9.2 software (Universität Kiel, Germany). We decided to enroll four extra subjects to each group to offset any dropouts. Thus, the total number of subjects in each group was 31. Statistical analysis was conducted using Statistical Package for Social Sciences for Windows (SPSS, Inc., Chicago, IL, United States) version 25.0. Numerical data were expressed as mean ± SD or median (interquartile range), while categorical data were expressed as numbers and percentages. Results were tested for normal distribution by Kolmogorov–Smirnov test. Categorical variables comparison was done using chi-square test between the four groups, while continuous parametric variables were compared using one-way analysis of variance, followed by post hoc analysis (Tukey’s test) for intergroup comparisons. Continuous nonparametric data variables were compared by Kruskal–Wallis test. All tests were two-tailed, and a P < 0.05 was considered statistically significant.

3. Results

130 patients were screened for eligibility to the study; six patients were ineligible. Four participants were excluded from the study, while two were declined from participation. Eleven participants were dropped out because of failed US-SCB, regardless of the cause. The remaining 113 patients were assigned randomly to Groups C (27 patients), M (29 patients), D (28 patients) and MD (29 patients) and completed the study protocol (Figure 1).

No statistical differences were noticed in demographic data (age, BMI and ASA) and surgical duration between the four groups (Table 1).

Adding magnesium or dexmedetomidine to the LA agent was found to lengthen its duration requiring for the first analgesic dose when compared to the control group, however adding magnesium to dexmedetomidine has shown to keep a prolonged time to first analgesia requirement when compared to using dexmedetomidine or magnesium alone, with significant difference between them (P < 0.001). The time to first analgesic dose was prolonged 2.2 times in Group MD, 1.7 times in Group D and 1.6 times in Group M as compared to in Group C with values of 20 ± 1.5, 15.6 ± 2.2, 14.4 ± 2.3 and 9 ± 1.5 respectively (Figure 2).

In 24 h, remarkable differences were noted between all four groups regarding the number of patients receiving paracetamol and ketorolac as postoperative analgesia and

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Figure 3: Visual analogue score over time in the studied group

Data are presented as median (IQR). Group C, control group; Group D, dexmedetomidine group; Group MD, magnesium + dexmedetomidine group

† Significantly lower compared to the control group (P < 0.001)
total amount of paracetamol and ketorolac consumption postoperatively. All patients in all groups required paracetamol as postoperative analgesia; however, only 33.3% of patients in Group C required ketorolac compared to 20.7% in Group M, 21.4% in Group D and zero in Group MD. Moreover, there was a noticeable decrease in consumption of paracetamol and ketorolac in Groups M, D and MD compared to Group C (*P < 0.001) (Table 2).

Intraoperative VAS scores showed no remarkable differences when comparing the three groups. Postoperative VAS scores showed no noticeable differences between the groups in the early 4-h period postoperatively. However, the postoperative VAS scores were remarkably increased in the Group C compared to those in Groups M, D and MD at 8, 12 and 16 h, while, at 16 hours, Group D’s score showed a noteworthy increase when compared to Group MD. There were no remarkable differences in postoperative VAS of the three groups at 20 and 24 h postoperatively (Figure 3).

The vital signs including MAP and HR were comparable intraoperatively at 15 min intervals and postoperatively without statistical significance.

No differences were noted in hospital stay nor the occurrence of intraoperative and postoperative complications in the three groups. At the end of surgery, most surgeons were satisfied with adding mixture of magnesium with dexmedetomidine to the LA agent compared to magnesium alone or dexmedetomidine alone. Moreover, the day after surgery, the patient satisfaction regarding the pain relief by this technique was remarkably high in Groups M, D and MD, compared to the control group (Table 3).

4. Discussion

In the current study, we conducted a SCB under US guidance to prevent damage to vas deferens or testicular artery. US-SCB is a simple, safe and reliable anesthetic technique for intracrotal surgery. It has provided...
excellent operating conditions and is a cost-saving technique, whether used in combination with a sedative or on its own. Furthermore, it provides early ambulation, minimal cardiac risks, satisfactory postoperative pain control and reduced hospital stay. Attempts were made to increase the length of analgesia provided by this block by addition of different agents. Therefore, in the present study, magnesium sulphate, dexmedetomidine and a combination of both were added to levobupivacaine to act as adjuvants in this block. It was shown that the mean duration of the first analgesic demand was notably increased when adding dexmedetomidine and magnesium to plain levobupivacaine 0.5%, compared to using magnesium sulphate or dexmedetomidine alone. Moreover, the amount of analgesic consumption postoperatively was significantly reduced when an adjuvant was used.

Levobupivacaine 0.5% shows less neural and cardiac toxicity when compared to bupivacaine, and is recently considered the closest to being the optimal agent for neural block; however, a high dose of the agent is needed to achieve an effective blockage.\textsuperscript{13,14}

Each adjuvant in our study has a specific mode of action, with a high level of safety and ability to prolong the pain-free duration. Dexmedetomidine prolongs the analgesic effect of the LA by causing local vasoconstriction, in addition to blocking the hyperpolarization-activated cation current. This leads to a direct impulse conduction inhibition in the peripheral nerves. It is a highly selective α2-adrenoceptor agonist, having more than seven times the affinity for α2 adrenoceptors than clonidine. Moreover, it can also be used as a sympatholytic agent and analgesic with minimal respiratory side effects. However, despite being a very promising adjuvant, it has limited use for its hemodynamic instability and high cost.\textsuperscript{10,15,16}

Conversely, magnesium sulphate is a physiological calcium antagonist exerting its actions by regulating the calcium influx into the cells and blocking the NMDA receptors, thus preventing the nociceptive stimulators to cause central sensitization, acquiring its antinociceptive effects. However, many studies claimed that using magnesium as an adjuvant caused a reduction in the postoperative pain in adults.\textsuperscript{11,17}

The current study revealed that the rate of success of the US-SCB using an adjuvant was improved in study groups in comparison to the control group.\textsuperscript{9,7,18}

Moreover, in our study, the mean time to the first analgesic dose was significantly increased with in the study groups in comparison to the control group.
However, the combined group showed the most prolonged duration postoperatively.

The results of our study agree with those of Sayed et al., who assessed using either dexmedetomidine or magnesium sulphate as adjuncts to bupivacaine for caudal block in children undergoing lower abdominal surgeries. The combined group showed the most prolonged period to first analgesic dose without difference between dexmedetomidine and magnesium sulphate groups.19

The findings of this study are in line with the observations of Yousef et al. who studied the time of first analgesic dose in 105 children undergoing herniorrhaphy. The time of first analgesic dose was notably increased in the group that where dexmedetomidine or magnesium sulphate was added to ropivacaine in the caudal block when compared to those who received ropivacaine only, without increasing the incidence of side effects.20 Similar studies were performed using 4 mL lidocaine 2% in peribulbar anesthesia, and ropivacaine in infra-clavicular brachial plexus block, prolonging the duration of sensory block.

However, dexmedetomidine showed side effects including intraoperative hypotension and bradycardia when compared to magnesium sulphate.21, 22

In the present study, there was no case of severe bradycardia or hypotension, which is considered in line with observations made by Saadawy et al., who claimed a non-statistically remarkable difference concerning hemodynamic changes when using dexmedetomidine in addition to bupivacaine versus bupivacaine alone for caudal block and general anesthesia.23

The mixture of magnesium sulphate and dexmedetomidine is considered an attractive choice as an adjuvant for local anesthetic due to the lack of major side effects like hemodynamic instability and respiratory depression.

5. Limitations

Despite achieving the study aims, we had some limitations: First, the level of intra- and postoperative sedation was not assessed. Second, the study was conducted for a single procedure. Finally, the level of the magnesium sulphate or stress hormone levels were not assessed. Thus, we recommend future research to evaluate the optimal doses of combined drugs and evaluate the efficacy for different types of procedures and blocks.

6. Conclusion

The combination of magnesium sulphate and dexmedetomidine as additives to levobupivacaine for ultrasound-guided spermatic cord block significantly prolongs the time of postoperative analgesia with decreased postoperative analgesic consumption, without significant drawbacks.

7. Data availability

All numerical data is available with the authors and can be provided on reasonable request.

8. Conflict of interest

None declared by the authors.

9. Authors’ contribution

ASW: Concept, design of the study, acquisition, analysis and interpretation of the data and drafting the manuscript

AAM: Concept, design of the manuscript, and revised it critically

MAF: Revised the manuscript critically.

AKS: Conduct of the study work

10. References


