Original Article

To assess the analgesic efficacy of adjuvant magnesium sulfate added with ropivacaine over ropivacaine alone as a continuous infiltration in total abdominal hysterectomy wound: A randomized controlled trial

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Abstract

Background and Aims: Magnesium sulfate ($MgSO_4$) has been demonstrated to have analgesic property in various clinical settings. This study explores if addition of $MgSO_4$ to ropivacaine increases its analgesic efficacy when infiltrated continuously in the postsurgical wound following total abdominal hysterectomy.

Material and Methods: This randomized controlled trial was conducted at a tertiary care referral hospital in New Delhi, India. Fifty-two patients were randomized into two groups to receive the intervention of which 48 were able to complete the study. The first group (n = 26) received 0.25% ropivacaine infiltration and the second group (n = 26) received 0.25% ropivacaine with 5% $MgSO_4$ at the incision site for 48 h postoperatively. Primary objective was to compare the total postoperative opioid (morphine) consumption by the study participants in both the groups and the secondary objectives were pain scores at rest and at movement, patient satisfaction score, and wound quality of life on the 7th postoperative day among the two groups.

Results: Both the groups were comparable in their demographic characteristics. The median morphine consumed at 48 h postoperatively was 16.5 [0–77] mg in the ropivacaine group and 13[1–45] mg in the ropivacaine with $MgSO_4$ group and the difference was statistically insignificant (P = 0.788). There was no statistical difference between the groups with respect to the pain scores, patient satisfaction, or wound quality of life at 7 days.

Conclusion: The addition of $MgSO_4$ to ropivacaine does not confer any additional postoperative analgesic benefits over ropivacaine alone in continuous wound infiltration following total abdominal hysterectomy.

Keywords: Acute pain, analgesia, magnesium sulfate, obstetric pain, postsurgical pain, ropivacaine

Introduction

Local anesthetic (LA) wound infiltration of surgical site often forms a part of the multimodal analgesic regime for acute postoperative pain management. The pain relief offered by this technique can be prolonged by infiltrating LA either as boluses or as a continuous infusion through catheters. Wound catheters have found acceptability, as it is a much simpler and more effective mode of pain control without the need for any additional intervention or expertise.

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Comparable pain scores were noted between continuous wound infiltration (CWI) and epidural analgesia for postoperative pain following abdominal surgery[1] as well as in thoracotomy pain management.[2] Wound infiltration has been demonstrated to have the same analgesic profile as paravertebral block or transversus abdominis plane (TAP) block.[3,4] A meta-analysis on the effectiveness of CWI has concluded it to be effective in reducing pain scores and opioid consumption in the postoperative period.[5] It is stated to be more effective in an obstetric and gynecological subset of patients.[6]

Ropivacaine is a well-established long acting amide LA with less systemic toxicity. The minimum concentration of ropivacaine at which pain relief is seen following wound infiltration is 0.25%.[7] Magnesium sulfate ($MgSO_4$) is a versatile drug with many clinical benefits. Its analgesic effect has been studied widely in recent years. Antinociceptive action of $MgSO_4$ has been attributed to the inhibition of calcium influx into cells and the antagonism of NMDA receptors.[8,9] Peripherally administered $MgSO_4$ was observed to have attenuated the transmission of noxious mechanical stimuli by acting on peripheral NMDA receptors.[10] Literature shows promising results in the form of decreased opioid consumption when administered via intravenous (IV) or intrathecal route.[8,9,11] Evidence related to its analgesic efficacy following tissue infiltration is not yet conclusive with limited literature approving it[12-15] while another study failed to show any benefit.[16] It has also been reported that rather than being a primary analgesic, $MgSO_4$ works best when added as an adjuvant to an established analgesic agent.[17,18] In the present study, we primarily aimed to compare the rescue analgesic requirement following infiltration of ropivacaine versus ropivacaine added with $MgSO_4$ in total abdominal hysterectomy (TAH) wounds. Secondary aims are comparison of pain and patient satisfaction scores along with wound quality of life, which has not been previously studied for CWI.

Research Hypothesis: The addition of $MgSO_4$ to ropivacaine will enhance its analgesic efficacy resulting in decreases in the amount of rescue analgesic (opioid) requirement when used for CWI after TAH.

Material and Methods

The Institute Ethics Committee (Ref No. IEC-419/02.09.2016, RP-18/2016) approved this study and the trial is in accordance with the Helsinki Declaration of 1975. Written and informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrolment at Clinical Trials Registry-India (CTRI/2017/07/009176).

Ours is a single-center, prospective, parallel-group, and randomized controlled trial. The trial was conducted at a tertiary care hospital. A total of 52 patients were randomly allocated to two groups (26 in each group) by computer-generated random number sequence. Allocation concealment was done by the Sequentially Numbered Opaque and Sealed Envelope technique. Inclusion criteria were female patients 1) 18 years and above; 2) belonging to American Society of Anesthesiologists Physical Status (ASA PS) I and II; and 3) undergoing open hysterectomy with a transverse incision (Pfannenstiel) for benign conditions. Exclusion criteria were patients 1) who refused to be part of the study; 2) having malignancy; 3) on systemic analgesic medication for some other ailment; and 4) known to have an allergy to any of the study drugs.

Patients who consented to be a part of the study were explained the functioning and care of the catheter and of the elastomeric pump a day before surgery. They were also explained about the patient-controlled analgesia (PCA) pump and taught how to use it for bolus doses. Verbal Rating Scale for Pain (VRSP) assessment was also explained. Oral pantoprazole 40 mg and oral alprazolam 0.25 mg were given on the night prior to surgery. In the operating room, standard monitoring devices, electrocardiography (ECG), noninvasive blood pressure (NIBP), and SpO_2 were attached to the patient and baseline vitals were recorded. Standard general anesthetic technique was applied to all patients with IV propofol 2 mg/kg and IV fentanyl 2 mcg/kg and IV atracurium 0.5 mg/kg. After securing the airway with a cuffed endotracheal tube, anesthesia was maintained with O_2, air, and isoflurane. IV morphine was given at 0.1 mg/kg after induction and IV acetaminophen 1 g was administered just before the closure of the wound. IV ondansetron 4 mg was administered approximately 20 min before tracheal extubation for prevention of postoperative nausea and vomiting. After the closure of the peritoneum, a continuous wound infiltration catheter was placed, above the peritoneum and beneath the transversalis fascia (preperitoneal space), along the entire length of the wound, by the surgeon. The catheter placement was aided by a split cannula of 18 G × 116 mm dimensions, which made a tunnel through the skin at about 5 cm lateral from the edge of the skin incision piercing the subcutaneous tissue, muscles, and fascia thus reaching the preperitoneal space, following which it was secured to the skin by suture and was under sterile dressing. The length of the wound was approximately 80–100 mm, hence we choose a catheter that had 30 holes in the first 75 mm so that the analgesic solution could be distributed evenly along the entire length of the surgical incision (InfiltraLong Set 500®, PAJUNK®; Geisingen, Germany). The catheter dimensions were 19G

and 500 mm long with a metallic helical coil embedded in the entire length of the catheter to avoid kinking. Taking all aseptic precautions an anesthetist, who was not a part of the study opened the sealed envelope with a random number and prepared the infiltration solution as per the instructions given inside and filled an elastomeric balloon pump (Fuser Pump®, PAJUNK®; Geisingen, Germany), which was then attached to the catheter, thus making the drug delivery a closed loop system. Wound was infiltrated with 10 mL of 0.25% ropivacaine as the first bolus dose. Continuous wound infiltration was activated immediately after shifting the patient to the postanesthesia recovery unit (PACU). The patients received one of the following two solutions as infiltrates for the next 48 h:

Group R: 0.25% ropivacaine at 5 mL/h

Group RM: 0.25% ropivacaine + 5% $MgSO_4$ at 5 mL/h

Preparation of infiltrate solution was made in the following way: For group R, 100 mL of ropivacaine 0.75% was mixed with 200 mL of 0.9% normal saline thus making it a solution with 0.25% ropivacaine. For group RM, 100 mL of ropivacaine 0.75% was mixed with 170 mL of 0.9% normal saline and 30 mL of $MgSO_4$ (50% w/v) thus making it a solution having 0.25% ropivacaine with 5% $MgSO_4$. A total of 300 mL of infiltrate was made for both groups, as that was the minimum quantity of the elastomeric pump used in the study.

All patients received intravenous morphine by PCA pump (Medima-S-PCA®, MEDIMA Sp.zo.o, Warsaw, Poland) for 48 h postoperatively. IV Morphine was administered at 1 mg per patient-controlled bolus with a 10 mins lockout interval with no baseline infusion. Maximum dose of morphine that could be taken over 4 h was set at 20 mg. Patients' heart rate, NIBP, ECG, SpO_2, and respiratory rate were monitored for 48 h postoperatively. In addition to the above IV acetaminophen 1 g was given at 6 hourly intervals to all patients. Patients were allowed to ambulate as per their wishes, and the urinary catheter was removed on the first postoperative day. Both the patient and the anesthetist collecting the data were unaware of the group allocation.

The primary outcome was to compare the total postoperative analgesic (morphine) consumed during the first 48 h. The secondary outcomes were to compare the VRSP at rest and mobilization (defined as pain experienced during coughing) at 2, 4, 6, 24, and 48 h (VRSP 0: No pain – 10 being worst pain experienced), patient satisfaction score at 48 h (using 4 point rating scale 1: poor, 2: fair, 3: good, 4: excellent), Wound Quality of Life at 7 days (using Wound-QoL questionnaire www.wound-qol.com)* *(Permission for using the questionnaire was obtained before finalizing the study protocol)

Patients were asked a set of 17 questions on the 7th postoperative day. The questions comprised of if the wound: hurt; had a bad smell; had a disturbing discharge; has affected sleep; the treatment of the wound has been a burden; has made her unhappy; felt frustrated because the wound is taking so long to heal; worried about the wound; afraid of the wound getting worse or of new wounds appearing; been afraid of knocking the wound; had trouble moving about; climbing stairs has been difficult; had trouble with day-to-day activities; has limited leisure; has forced to limit activities with others; felt dependent on help from others; and has been a financial burden.

We categorized the response to the questionnaire in numerical values: 1 (not at all); 2 (a little); 3 (moderately); 4 (quite a lot); and 5 (very much).

Sample size calculation

Eldaba *et al.*[19] reported the mean ± SD opioid requirement over 24 h as 25 ± 7.5 mg and 10 ± 4.5 mg in two groups of patients using bupivacaine and bupivacaine with $MgSO_4$, respectively, in patients undergoing cesarean section (CS). We anticipated double the amount of requirement over 48 h.

We wished to demonstrate the CWI of ropivacaine with $MgSO_4$ to be superior to ropivacaine alone in patients undergoing TAH. The true difference between the two drugs was assumed to be 15 mg with a combined SD of 5.9 mg. With 90% power and 5% level of significance, the required sample size to establish the superiority of ropivacaine with $MgSO_4$ was 24 per group. Considering potential dropouts during the course of the study we kept two patients extra in each group making a total of 52 patients in the study.

Statistical analysis

The statistical analysis was carried out using Stata 12.0 (College Station, Texas, USA).

Data are presented as Mean (SD)/Median (Q1 - Q3) and frequency (%). Mean difference and 95% confidence interval for opioid consumption between the groups at 48 h were calculated. Continuous variables were compared using *t* test/Wilcoxon rank-sum test as appropriate and within-group change in the continuous variables was assessed by Generalized Estimating Equation (GEE) analysis.

Categorical variables were compared among the groups by Chi-square/Fisher's exact test. Other appropriate statistical analyses were carried out at the time of analysis. *P* value less than 0.05 was considered statistically significant.

Results

The consort flow chart is shown in Figure 1. A total of 63 patients were assessed for eligibility, four patients did not meet the eligibility criteria, further five more patients refused to give consent to be study subjects, and surgery was deferred for two patients. Four patients got excluded from the study after receiving intervention of which one needed re-exploration after 24 h due to unexplained abdominal distension and in the second, the wound catheter accidentally got dislodged while ambulation. In another patient, the PCA pump started malfunctioning and was detected after the lapse of a few hours. And in the fourth patient, additional analgesics other than the study protocol were prescribed. Finally, data from 24 patients in each group were statistically analyzed. Patients were recruited from August 2017 till December 2019 and followed up till December 2020.

The demographic data and the duration of surgery of both groups were comparable as represented in Table 1.

The total amount of postoperative morphine consumed in the form of rescue analgesia at 48 h was slightly higher in the ropivacaine group than in the ropivacaine and $MgSO_4$ group but the difference was statistically insignificant as depicted in Table 2. Statistical comparison of pain scores (VRPS) at rest and at movement revealed insignificant difference between the ropivacaine group and ropivacaine and $MgSO_4$ group at all the measured time points, as depicted in Figures 2 and 3. Patient satisfaction was comparable with a statistically insignificant difference between the two study groups at 48 h as shown in Table 3. Vital parameters were within acceptable limits with no significant difference between the two groups as compared with GEE population-averaged model (Heart Rate [$P = 0.85$], Diastolic blood pressure [$P = 0.60$], systolic blood pressure [$P = 0.92$], Respiratory rate [$P = 0.25$], and SpO_2 [$P = 0.81$]) Wound QoL on the 7th postoperative day: None of the patients in any of the groups answered in category 4 (quite a lot) or 5 (very much). All the responses were in category 1 (not at all) or 2 (very little).

Although not a part of our study, we telephonically followed up with the patients at 6 months and 1 year after surgery. We lost eight patients to follow-up, as we were unable to contact them with hospital records. Of the 40 others, four patients (1 from the ropivacaine group and 3 from the ropivacaine with magnesium group) still could feel mild tingling pain at the incision site, but did not require analgesics and did not have any untoward effect on daily activities. No adverse effects were noted in any of the participants during the course of the study.

Discussion

The addition of $MgSO_4$ to ropivacaine reduced the rescue analgesic consumption as compared with ropivacaine alone following CWI in patients undergoing TAH in our study, but

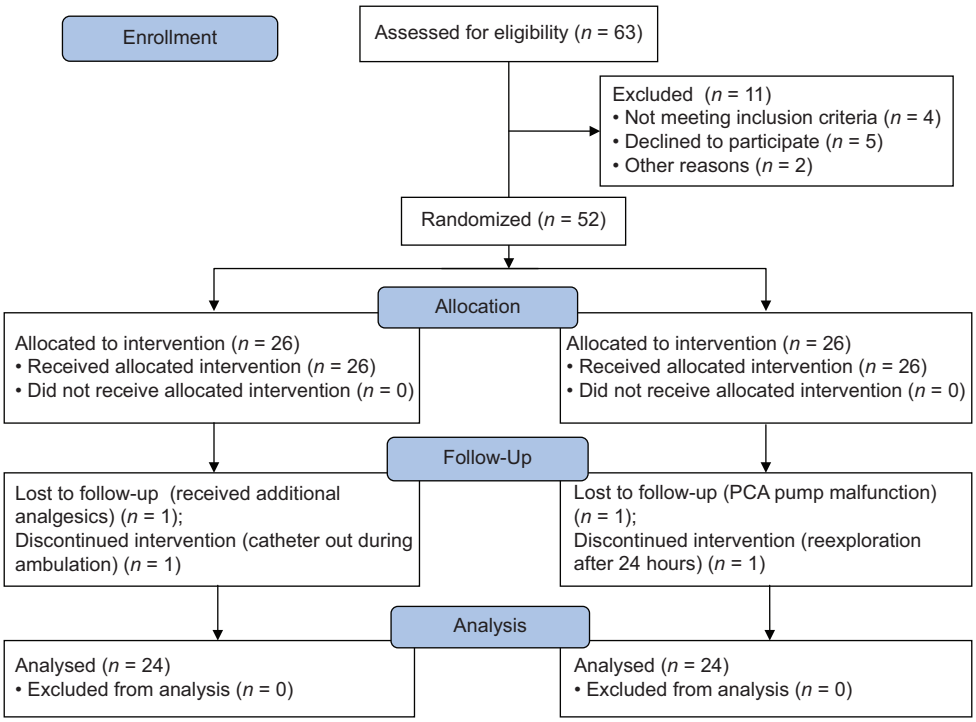

Figure 1: CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials

Table 1: Demographic data

	Group: Ropivacaine (*n*=24)	Group: Ropivacaine + $MgSO_4$ (*n*=24)	*P*
Age (mean±SD)*, years	42.6±10	43.9±7.5	0.60
Weight (mean±SD), kg	57.5±10.24	60.45±9.38	0.30
ASA PS (Frequency %)**			
I	19 (79.17)	17 (70.83)	0.50
II	5 (20.8)	7 (29.17)	
Duration of surgery (mean±SD)*, h	1.83±0.38	1.6±0.47	0.08

**t-test **Fisher's exact test; SD, standard deviation*

Table 2: Total Opioid Consumption at 48 h

	Group: Ropivacaine (*n*=24)	Group: Ropivacaine + $MgSO_4$ (*n*=24)	*P*
Median [Q1–Q3][&], mg	16.5[5.5–33.5]	13[11–27]	0.788

[&]Wilcoxon rank-sum test

Table 3: Patient Satisfaction Score

	Group: Ropivacaine (*n*=24)	Group: Ropivacaine + $MgSO_4$ (*n*=24)	*P*
2 (Frequency %)**	3 (12.5)	0	0.12
3 (Frequency %)**	5 (20.83)	10 (41.67)	
4 (Frequency %)**	16 (66.67)	14 (58.3)	

***Fisher's exact test*

in a statistically insignificant way. Pain scores both at rest and movement were similar and there was no difference either in patient satisfaction score at 48 h or in Wound-QoL at 7 days postoperatively in both groups.

Comparison of the total amount of rescue analgesic consumed in absolute terms is difficult as the studies available are heterogeneous in methodology in terms of the site of catheter placement, the volume, and the concentration of drugs used.

$MgSO_4$ infiltration has been shown to enhance analgesia when added to a long-acting LA[19,20] or even when used as a sole agent.[12] Majority of the studies that have added $MgSO_4$ to LA for CWI in the subfascial plane[19] or as a single bolus in the skin and subcutaneous tissue[20] in CS (pfannenstiel incision) or following radical prostatectomy,[13] sternotomy,[14] or lumbar laminectomy[15] have reported of a significant reduction in opioid consumption as compared with infiltration with LA alone. Our study also showed improved analgesia after the addition of $MgSO_4$ to LA but statistically, it was insignificant.

Our study was in congruence with the study by Imani *et al.*,[21] where the addition of $MgSO_4$ to ropivacaine decreased rescue analgesic consumption only in an insignificant way as compared with ropivacaine when used for TAP block in patients undergoing TAH.

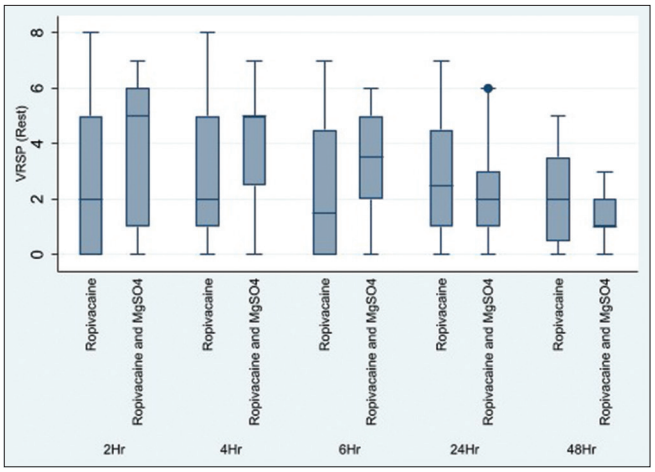

Figure 2: VRSP at rest. VRPS indicates verbal rating scale of pain

The choice of preperitoneal—subfascial catheter and the concentration and volume of drug used in our study were both reasonable and justified when compared with other studies on CWI in the subfascial plane,[22-25] superficial to fascia or in subcutaneous tissue.[26-28]

Although the ideal plane of catheter insertion for surgeries done with Pfannenstiel incision is not yet clear, the current evidence is somewhat inclined toward subfascial/preperitoneal catheter as supported by studies[23,29-31] and meta-analyses.[1,32,33]

Unlike our study, significant decreases in pain scores were reported after addition of $MgSO_4$ to LA as compared with LA only in wound infiltration following CS[19] and sternotomy[14] and radical prostatectomy.[12] Comparable pain scores with or without the addition of $MgSO_4$ to LA after one-time infiltration were seen in cesarean section[20] and radical prostatectomy[13] and following TAP block in TAH patients[21] and these results are in congruence with our study.

Patient satisfaction has been high in both our groups and across studies that have compared wound infiltration using different infiltrate solutions or compared wound catheters with other modalities of pain control.[3,22,28,34]

The use of catheters for CWI has not been reported to be associated with any wound-related complications

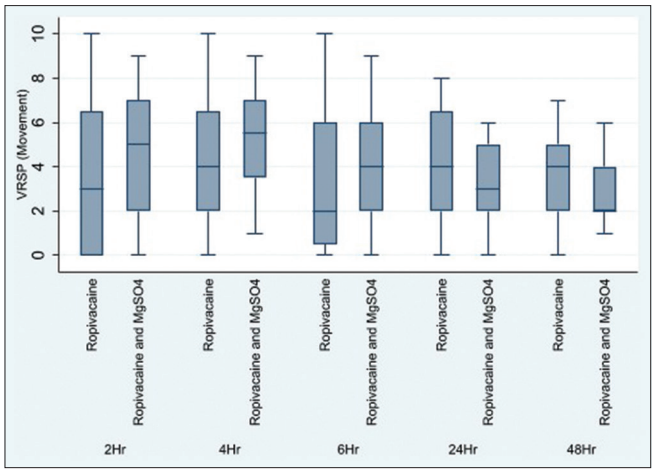

Figure 3: VRSP at movement. VRPS indicates verbal rating scale of pain

like dehiscence or infection in the literature that we searched.[22,25-27,29,34,35]

In the current study, all patients in both groups had very little pain without having any effect on daily life activities. The problem that we encountered related to the use of wound catheter was kinking of the catheter with no flow, which was due to the use of artery forceps to hold the catheter while placing. This was diagnosed before the wound closure, as we routinely do a patency check by injecting saline before the suturing of the wound.

The limitation of the study is for being a single-center study. Also, the exact role of $MgSO_4$ in visceral and somatic pain is not fully established hence we cannot write off its analgesic effects based on a single study where the drug was infused in only one neurovascular plane. The cost of the catheter and the pump is high hence their use may have to be restricted to patients where neuraxial blocks are contraindicated or difficult or in the presence of comorbidities, which restricts generous use of opioids or nonsteroidal anti-inflammatory drugs.

Conclusion

Although statistically insignificant, the addition of $MgSO_4$ to ropivacaine confers additional postoperative analgesic benefits over ropivacaine alone in continuous wound infiltration following total abdominal hysterectomy.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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Conflicts of interest

There are no conflicts of interest.

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