Short Communication

Intravenous Versus Epidural Magnesium Adjunct on Postoperative Pain in Patients Receiving General Anaesthesia For Abdominal Surgery

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ABSTRACT

Background: Although, magnesium is a potent postoperative analgesic adjunct, its most effective route of administration is undetermined.

Patients and Methods: Fifty-two patients, aged 18 – 65years, with American Society of Anesthesiologist (ASA) I and II, were randomised into three groups. Group A received IV 50 mg/kg magnesium and placebo epidural; group B (Epidural) received IV placebo and 250mg magnesium epidural, while group C (Control) received both IV and epidural placebo. The postoperative analgesic profile was recorded.

Results: Socio-demographic indices were comparable. The time to first request for rescue analgesics was statistically longer in epidural magnesium, 660±20 mins, versus IV, 540±30 mins, while both were longer than placebo, 380±20 mins, (p-value 0.02). The mean rescue doses were statistically lower in epidural magnesium, 1 (5%) versus IV magnesium, 2 (13%) and placebo, 3 (17%), p-value 0.001. The mean total 24-hours rescue morphine consumed were lower with epidural magnesium, 1.12±1.04mg, versus IV, 1.18±0.82mg and in turn, versus lower than placebo, 3.02±0.84mg, p-value 0.04.

Conclusion: Epidural magnesium is better than IV, in extending postoperative analgesia duration, and reducing both rescue doses and the total 24-hours rescue opioid consumed.

Keywords: magnesium, abdominal surgery, epidural, intravenous, postoperative pain, analgesia

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INTRODUCTION

Despite progress in pain medicine, the incidence of disturbing postoperative pain is high. An African study reported 83.9%.[1] Inadequate postoperative analgesia leads to poor ventilatory effort, ineffective cough and sputum clearance, leading to hypoventilation, acidosis, hypoxia, chest infection, and respiratory failure.[2,3] Activation of sympathetic nervous system (SNS), catecholamines and inflammatory mediators promote tachycardia, vasoconstriction and hypertension lead to angina, myocardial infarction and arrhythmias. Other pain complications are sodium and water abnormalities, hypercoagulability, insulin resistance, and urinary retention. Adequate analgesia increases return to pre-morbid function.[3,4,5]

Magnesium's analgesic action is linked to the blockade of N-methyl-D-aspartate (NMDA) receptor and calcium ion entry.

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Magnesium had extended analgesia via the intravenous (IV), spinal, epidural, peritoneal, wound infiltration, intra-articular, topical, and peripheral nerve blockade routes.[6] Perhaps, the IV[7,8] and epidural[9,10] routes are the most studied. However, its most effective route is un-known. Curiously, a study that directly compare the analgesic effects of IV magnesium adjunct versus epidural is sparse.

Our objective is to compare the time to first request for rescue analgesics, the mean rescue dose administered and total rescue opioids consumed between IV and epidural magnesium.

SUBJECTS AND METHODS

Ethical approval/study period: This prospective, randomised, double-blinded study was approved by the Research and Ethics Committee of the Obafemi Awolowo University Teaching Hospital, with protocol number ERC/2023/03/08, and conducted between April and September, 2023.

Inclusion criteria: Patients aged 18 and 65 years, ASA I and II, who had elective abdominal surgeries, under general anaesthesia (GA) with tracheal intubation (TI), were enrolled.

Exclusion criteria: Patients who refused consent, had drug allergy, full stomach, extended surgeries, severe cardiac, respiratory, or renal disease, behavioural illness, hypercoagulability, sepsis, bleeding disorders, body mass index (BMI) $\geqslant$ 35 kg/m^2, long-term use of opioids, magnesium, or calcium blockers, or contraindications to epidural block were excluded.

Randomisation: A computer-generated table of random numbers was drawn by a statistician. Block randomisation, in groups of fives, was used to ensure even distribution. The numbers were coded into three groups.

For each patient, the statistician identifies the coded number, linked it to the group, and inform the pharmacist, who prepared the IV and epidural drugs. The pharmacist gave the drugs to the Anaesthetist at the red line. Thus, the patients and Anaesthetists (investigators) were blinded. The statistician, who was not-blinded, did the un-coding after the study.

The IV drugs were prepared in 100ml in fluid bag. The epidural drugs were prepared in 15ml, drawn into 20ml syringe. Drugs were colourless. Both drugs were given within 15 mins before induction.

Patients in group A (IV) received IV magnesium and epidural placebo; i.e., IV 50mg/kg magnesium in 100ml sterile water and epidural admixture of 1ml saline plus 1ml fentanyl 50µg plus 13ml plain bupivacaine 0.125%, to make 15ml volume.

Patients in group B (Epidural) received IV placebo and epidural magnesium i.e., IV 100ml sterile water and epidural admixture of 1ml magnesium 250mg plus 1ml fentanyl 50µg plus 13ml plain bupivacaine 0.125 %, to make 15 ml volume.

Patients in group C (Control) received IV placebo and epidural placebo, i.e., 100ml sterile water and epidural admixture of 1ml saline plus 1ml fentanyl 50µg plus 13ml plain bupivacaine 0.125%, to make 15ml volume.

Sample size: was calculated using the formula by Chindanand et al.[8] In previous studies, IV[9] and epidural[10] magnesium had extended postoperative analgesia by 43.5% and 63.1% respectively, with mean of 53.3%. Using α - 0.05, β - 0.1, δ - 8.5, σ - 120 minutes, power - 80%, probability of type I error - 5%, the sample size of 80 patients was determined.

$$n = \frac{2(Z\alpha + Z\beta)^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

$$\frac{2 \times (1.96+0.84)^2 \times (120)^2}{(53.3)^2}$$

$$n = \frac{225792}{2840.89}$$

n = 79.47 Approximately 80

n = minimum sample size of each arm of the study group.

α = probability of making type I error.

β = probability of making type II error.

$Z\alpha$ = 1.96 for a two-tailed test (standard normal deviate).

$Z\beta$ = 0.84 (at 80% power)

σ = standard deviation =120

$\mu_1 - \mu_2$ = difference between the two groups that the study hopes to detect. (53.3)

Recruitment: All patients were recruited during the pre-anaesthesia visit. History, examination and investigation results were reviewed. All patients were fasted and consented.

Study Protocol: On the morning of surgery, the Anesthesia machine were checked. All drugs were drawn and labelled appropriately.

First, while on the operating table, patient's baseline vitals were recorded using the pulse oximetry, electrocardiograph (ECG), and the non-invasive blood pressure (NIBP). Venous access was gained with size 16/18G cannula. Epidural catheter was positioned, asterile, and in sitting position. Thereafter, patient was placed supine.

Next, the IV and epidural drugs were given simultaneously. The Anaesthetist open the 100ml IV drip, and also gave the epidural with 20ml syringe, slowly over 15 minutes, which is timed by an assistant using a stop-clock.

Thereafter, induction of anaesthesia was done. Patient was preoxygenated with 100% oxygen for five minutes. Midazolam 2 – 4 mg and propofol 100 – 140mg IV was used for induction. Pancuronium 6mg was given to facilitate intubation. Time was allowed for depth. Tracheal intubation was done using tracheal tubes (TT) 7.0 - 7.5 mm (female), and 7.5 - 8.0 mm (male), and confirmed with auscultation and capnography. The tube was connected to Anaesthesia

machine via the circle breathing system. Anaesthesia was maintained with isoflurane MAC 1 – 2 % in 60 – 100% oxygen. Pancuronium 2mg aliquot, every 30–40 mins, was used for muscle relaxation. Paracetamol 1000mg and fentanyl 50µg IV were given as analgesics. Intraoperative haemodynamics, euvolaemia, normocapnia, and normothermia were maintained.

After the surgery, wound infiltration was done using 10 – 15ml plain bupivacaine 0.25%. The vapourizer was tuned off. Neostigmine 2.5mg and glycopyrrolate 0.2mg IV were administered as reversal, and TT was removed after airway suctioning. Afterwards, supplemental oxygen was given and the patients were transferred to the recovery room. Saturation, breathing effort, level of consciousness, and haemodynamics were monitored. Paracetamol IV 1000mg 6 hourly, and diclofenac IV 50mg 8 hourly were commenced. Patients were transferred to the ward following the modified Aldrete's score satisfaction.

Outcome: Rescue analgesic was provided, with IV morphine 1mg, (at not less than) 6 hours interval. The time to the first request of rescue morphine, the number of rescue doses demanded and total rescue morphine consumed over 24 hours were recorded.

Statistical Analysis: Data collected with proforma, were analysed using SPSS 24.00 version software (IBM). Categorical data (i.e., sex, ASA physical status, and number of rescue doses) shown in frequencies and proportions were analysed using the Chi squares test. Quantitative data (e.g., age, weight, height, surgery duration, time to first rescue analgesic, total analgesic consumed) shown as mean and standard deviation, were analysed with student t-test. Inter-group data were analysed as A-B, B-C, and A-C. The p-value < 0.05 was considered statistically significant.

RESULTS

The demographic parameters, i.e., age, sex, and ASA were comparable, p-value > 0.05 (Table 1). The mean time to first

Table 1: Socio-demographic parameters and duration of surgery

	Group A N=16	Group B N=18	Group C N=18	A-B	B-C	A-C	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**t value**	**t value**	**t value**	
Mean Age (18 - 45 years)	29 ± 11	36 ± 9	30 ± 10	0.784	0.573		0.277
ASA	N (%)	N (%)	N (%)	X^2 value	X^2 value	X^2 value	
I	7 (44)	6 (33)	13 (72)	0.862	0.978	0.577	0.545
II	9 (56)	12 (67)	5 (28)	0.535	0.729	0.783	0.473
Sex							
Male	5 (31)	7 (39)	8 (44)	1.211	0.837	1.012	0.366
Female	11 (69)	11 (61)	10 (56)	0.992	0.772	0.692	0.902
Anthropometrics	Mean ± SD	Mean ± SD	Mean ± SD	t value	t value	t value	
Weight (kg)	62 ± 7	71 ± 6	70 ± 5	0.997	0.936	0.578	0.617
Height (m)	1.5 ± 0.3	1.6 ± 0.1	1.5± 0.2	0.788	1.002	0.965	0.866
Surgery (mins)	150 ± 10	150 ± 10	160 ± 10	0.431	0.767	0.814	0.395

N: Number of patients in each group; %: Percentage; SD: Standard deviation; ASA: American Society of Anesthesiologists
t value:Independent Student t-test value; X^2 value:Chi-square value

Table 2: Profile of postoperative analgesia

	Group A	Group B	Group C	A - B	B - C	A - C	p-value
	N=16 Mean ± SD	**N=18 Mean ± SD**	**N=18 Mean ± SD**	**t value**	**t value**	**t value**	
Time to first request for rescue analgesics (mins)	540 ± 20	660 ± 30	360 ± 20	0.433	0.161	0.122	0.02
	n (%)	n (%)	n (%)				
Mean number of rescue doses	2 (13)	1 (5)	3 (17)	0.112	0.011	0.001	0.001
Total Mean total rescue Morphine 1 mg, consumed	1.18 ± 0.82	1.12 ± 1.04	3.02 ± 0.84	0.243	0.327	0.121	0.04

n = Number of subset; N = Total number in the population

request for rescue analgesics was statistically longer in group B, 660±20mins, compare to group A, 540±30mins, and both are longer than group C, 380±20mins, p-value 0.02. The mean rescue doses were statistically lower in group B, 1 (5%) versus group A, 2 (13%) and in turn, both are lower than group C, (17%), p-value 0.001. The mean 24-hours total rescue morphine consumed was statistically more in group C, 3.02±0.84 mg, versus group A, 1.18±0.82mg, and in turn, both are more than group B, 1.12±1.04mg, p-value 0.04 (Table 2).

DISCUSSION

Due to rising age and population, the incidence of abdominal surgeries is increasing worldwide. However, ineffective pain-relief is a drawback in sub-Saharan Africa.[11] Inadequate analgesia reduce restoration to pre-surgical physiology and worsen patient's morbidity.[1,3,11]

Postoperative pain promotes deep venous thrombosis, prolonged immobilisation, postoperative nausea and vomiting, hyperglycaemia, nosocomial infection, and fluid and electrolyte imbalance, which increase hospital length of stay, and cost. Chronic pain, mental distress and depression are long-term sequalae.[1,11] Effective postoperative analgesia reduces inflammatory, metabolic, and neuroendocrine stress responses to surgery.[5,11]

In this study, the time to first request for rescue analgesics is the postoperative analgesia period.

First, we report that the mean postoperative analgesia duration was longer in epidural magnesium 660±20 mins by 22%, more than IV, 540±30 mins, reduced mean rescue doses, 1/15 versus 2/17, and lower the 24-hours rescue morphine consumed 1.12±1.04mg, by 5%, versus IV magnesium 1.18±0.82mg, in placebo.

This is not surprising. Though not a direct analgesic agent, magnesium's anti-nociceptive function has been demonstrated. Magnesium blocks the NMDA receptor, a ligand-gated ion channel, in a voltage-dependent manner. The NMDA receptor is present in brain, spinal cord, peripheral nerves and other tissues. Pain is propagated when glutamate agonist binds to the receptor and facilitate sodium and calcium ion cellular inflow and potassium outflow.[4] The NMDA receptor promotes (1) winding-up and potentiation, via frequent and continuous C-fibre depolarisation, and (2) central sensitisation, via increased dorsal horn excitability. These processes cause pain hypersensitivity. Thus, the NMDA receptor blockade produce analgesia.[4,5,6]

The epidural route of administration appears to be superior in blocking visceral and somatic pain, since the fibers travel via the spinal column after abdominal surgeries.[5]

Similarly, Elsharkawy et al[9] reported that in pelvic surgeries, 100mg epidural magnesium extended postoperative analgesia 13.7±1.01hrs by 62%, versus 8.48±0.82hrs and lower rescue opioid consumed 4.3±0.7ml by 176%, versus 11.9±1.4ml, in placebo. Salman et al[10] stated that 50mg epidural magnesium, extended postoperative analgesia 3.9±0.37hours by 44%, versus 5.6±0.96hrs, reduce rescue doses 2/28 versus 3/27 and also reduce total Pethidine consumed, 105.0±15.3mg, by 39%, versus 146.7±12.7mg in placebo. de Oliveira Filho et al[12] in a systematic review stated that epidural magnesium significantly extended the postoperative analgesia and reduced the 24-hours rescue opioid consumed compared to placebo.

Secondly, while we report that on one hand the postoperative analgesic profile of epidural magnesium adjunct is better than IV, on the other hand, IV magnesium is better than placebo. Similarly, Chindanand et al[8] stated that IV magnesium 50mg/kg extended postoperative analgesia, 436.18±53.88mins by 86%, versus 234.00±30.31min in placebo, after infra-umbilical surgeries. Yazdi et al[7] showed that IV magnesium 25 mg/kg reduce rescue morphine consumption 8±3.5mg, by 65%, versus placebo 13.2±5.7mg, after abdominal surgeries. Oernskov et al[13] in a systematic review, reported that IV magnesium reduced postoperative morphine used versus placebo.

Thirdly, we showed that magnesium adjunct has opioid-sparing properties. This is useful in low-resourced environments, with limited tools to manage opioid problems, such as sedation, ventilatory depression, nausea, and vomiting.[11,14] Also, our experience is that magnesium is low-cost and accessible.

Multimodal analgesia was employed in this study. Our patients had regional block, wound infiltration, and parenteral paracetamol and NSAIDs. The use of two or more drugs with different actions and techniques, limit side effect, and optimise analgesia.[5]

To our knowledge, we did not find a literature that directly compared the effects of IV versus epidural magnesium adjunct on postoperative analgesia. Our study is unique in this wise.

Also, we did not record signs of magnesium toxicity.[15] However, our patients were placed on surveillance for dizziness, absent tendon reflexes, oliguria, hypoventilation or cardiac arrest. Management included 10 ml of 10 % calcium gluconate, and if needed, haemodialysis, ventilatory or cardiac support.[16]

CONCLUSION

This study shows that epidural 250mg magnesium extended postoperative analgesia period and reduced 24-hours rescue opioid use, better than IV magnesium.

The limitation is that industrial actions and cost of epidural kit, reduced our study population. Also, the patient-controlled

analgesia (PCA) device was inaccessible, in our institution, at the time of the study.

We recommend that clinicians may consider epidural magnesium to prolong postoperative analgesia and spare rescue opioids use, to enhance recovery in patients undergoing abdominal surgeries.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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