Original Article

Effect of magnesium and lignocaine on post-craniotomy pain: A comparative, randomized, double blind, placebo-controlled study

ABSTRACT

Background: Lignocaine and Magnesium have an analgesic action and reduce perioperative opioid requirements. We carried out this study to evaluate the effect of magnesium and lignocaine on postoperative pain as assessed using the visual analog scale (VAS) and fentanyl consumption. We also measured S-100 B levels and noted the side effect of drugs if any.

Materials and Methods: In this prospective preliminary study, 45 patients undergoing supratentorial craniotomy for tumor surgery were randomized to receive either lignocaine (group I-1.5 mg/kg bolus followed by 2 mg/kg/h infusion), saline (Group II) or magnesium (group III: bolus of 50 mg/kg followed by 25 mg/kg/hr) intraoperatively. The amount of fentanyl required, VAS over first 24 hours and any side effects were noted. S100 B levels were also measured to assess brain protective effect of these drugs, if any. Appropriate statistical tests were applied for analysis of data and a P value < 0.05 was considered statistically significant.

Results: None of the patient experienced any adverse hemodynamic effect intraoperatively secondary to the study drugs. The amount of intraoperative fentanyl consumption was comparable among the three groups. The mean VAS score was significantly less in group I and III [Group I (15.3 ± 6.0), Group II (24.8 ± 6.7), Group III (17.9 ± 7.6); (P < 0.01)]. The fentanyl consumed in first 24 hours was significantly less in those patients who received lignocaine and magnesium [Group I (204.4 ± 136.4), Group II (383 ± 168.2), Group III (194 ± 148.9); (P = 0.01)]. S100 value did not differ in the lignocaine and the saline group during the perioperative period. However, a significant decline was noted in the levels of S100 B in the magnesium group.

Conclusion: Intraoperative infusion of lignocaine and magnesium results in lower VAS score and decreases the postoperative opioid requirement in patients undergoing craniotomy for excision of supratentorial tumors.

Key words: Lignocaine; magnesium; post craniotomy pain; visual analog scale

Introduction

Until recent times, post-craniotomy pain was not a well appreciated entity and the concern of neurological deterioration often made the treating physician wary of opioids. Ineffective treatment of pain causes increased sympathetic activity leading to increase in blood pressure, cerebral blood flow, cerebral oxygen consumption, and intracranial pressure. Increased blood pressure may produce cerebral edema or even intracranial bleeding. Adequate

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postoperative analgesia can therefore reduce complications and shorten recovery.

Various drugs like paracetamol, tramadol, diclofenac, gabapentin have been used along with opioids for analgesia in these patients.[1,2] To decrease the dose of opioids, multimodal approach to pain is the preferred technique. Magnesium being antagonist at NMDA receptor has a potential analgesic action.[3] Similarly, intravenous lignocaine has been used during intra-operative period for decreasing the dose of analgesics and better post-operative recovery.[4,5] In addition to their analgesic action, these drugs also have a cerebral protectant potential.[6,7] S-100 is a calcium binding protein having α and β subunits. The β subunit is present mainly in glial and schwann cells, level of which increases in blood after variety of brain injury and is associated with poor outcome.[8] These two drugs have been used in various types of surgeries and have been found to reduce peri-operative opioid requirements. But, their comparative study in patients undergoing craniotomy for supratentorial tumours has not been performed to date. Therefore, this study was undertaken to compare the analgesic efficacy of magnesium and lignocaine in patients undergoing craniotomy for supratentorial tumors. Our primary objective was to evaluate the effect of magnesium and lignocaine on postoperative pain as assessed using the visual analogue scale (VAS). Our secondary outcomes were to determine total fentanyl consumption, (intraoperatively and 24 hours postoperatively), to assess the S-100 B levels and to study side effects of drugs if any. We studied the values of S100 B protein as a marker of neuroprotective effect of these drugs.

Materials and Methods

The study was carried as a preliminary, randomized, placebo-controlled, double-blind study. Approval of the study protocol from the Institutional Ethics Committee was obtained and a legitimate, written, informed consent for participation in the study was obtained from all patients. This was registered at clinical trial.nic.in (CTRI/2016/08/007168). Our primary objective was to evaluate the effect of magnesium and lignocaine on postoperative pain as assessed using the visual analog scale (VAS). Our secondary outcomes were to determine total fentanyl consumption, to assess the S-100 B levels and to note side effects of drugs if any.

In this preliminary study, we enrolled 45 patients undergoing supratentorial craniotomy for tumour excision in this study, carried over a period of one year. Patients aged 18-60 years, ASA physical status I and II, with Glasgow coma scale (GCS) of 15 undergoing elective craniotomy were included in this study. Patients with cardiovascular (such as atrio-ventricular block), respiratory, hepatic or renal disease, on treatment with calcium channel blockers, mental disability; who had a brain tumor larger than 30 mm in any dimension, patients with neurological/cognitive deficits (precluding their use of a patient-controlled analgesia [PCA] device), and patients with known allergy to any of the study medications or history of myopathy or substance abuse were not included in this study. Those patients who were not tracheally extubated and mechanically ventilated in the postoperative period were excluded from the final analysis.

A thorough general and systemic examination was performed a day prior to the surgery and all significant details were noted. The use of patient controlled analgesia (PCA) device and the 100 mm visual analog scale (VAS) for pain VAS (0 = no pain to 100 = worst imaginable pain) were explained to the patients during the preoperative visit. An adequate period of fasting was ensured before shifting the patients to the operating theatre (OT). Patients meeting the inclusion criteria during the pre-anaesthetic evaluation were randomly assigned into three groups of 15 each with the help of a computer-generated table of random numbers. Allocation was performed using sequentially numbered opaque sealed envelopes. For blinding, all the study drugs were prepared in identical syringes (10 ml for bolus administration and 50 ml for infusions) by an anaesthesiologist not involved in study, in a manner that rate of infusion was kept constant at 6 ml/kg/hr (by varying the dilution) in all the three groups.

The patients received either magnesium or lignocaine or 0.9% normal saline as placebo and were closely watched for any symptoms of possible adverse effect of study drugs such as ECG changes, prolonged neuromuscular paralysis, or delayed awakening:

Group I – Patients were given Lignocaine bolus of 1.5 mg/kg lignocaine over 15 min, followed by infusion of 2 mg/kg/h (6 ml/hr).

Group II - Patients were given a 10 ml bolus of 0.9% normal saline over 15 min, followed by an infusion of 6 ml/hr.

Group III – Patients were given Magnesium sulphate (50%) 50 mg/kg over 15 min, followed by infusion at the rate of 25 mg/kg/hr (6 ml/hr).

After securing an intravenous access, non-invasive monitoring (5-lead electrocardiography, pulse oximetry and automated noninvasive blood pressure) was commenced. Neuromuscular monitor was attached and 'BIS' electrodes

(BIS QUATRO - BX13366, Aspect Medical Systems, Inc. USA) was applied on the side opposite to planned craniotomy. A blood sample for S-100 B protein, level estimation was collected. Enzyme-linked immunosorbent assay (ELISA) kits were used for estimation of S100 B protein plasma levels. A bolus of study drug was administered over 15 mins before induction of anaesthesia followed by intravenous infusion at rate of 6 ml/hour till the last surgical suture was applied. Anaesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg. Muscle relaxation was achieved with rocuronium 1 mg/kg. After the tracheal intubation, mechanical ventilation was started to maintain PaCo2 at level of 33-35 mm Hg. Maintenance of anaesthesia was carried out by continuous infusion of propofol (6-8 mg/kg/h) along with oxygen (40%): air (60%) mixture with flow rate of 2 l/min, titrated to maintain the 'BIS' value within 50-60. Intermittent boluses of rocuronium (0.05 mg/kg) were administered for maintenance of muscle relaxation. Fentanyl bolus 1 μg/kg was administered every hour or if in the BIS range of 50-60, heart rate or blood pressure increased 25% above baseline. Temperature monitoring was done performed using nasopharyngeal probe. Arterial cannulation of dorsalis pedis or posterior tibial artery for measurement of invasive blood pressure was performed in all the patients. HR and MAP were maintained within 20% of baseline. Hypotension or hypertension (taken as fall or increase in MAP by >20% from baseline respectively) lasting for more than a minute was treated with bolus of mephentermine and esmolol respectively. Intraoperative events, if any were recorded. Residual neuromuscular block was reversed using neostigmine 0.06 mg/kg and glycopyrrolate 0.02 mg/kg. Total intraoperative fentanyl used, duration of surgery, anaesthesia, time to awakening (stopping of propofol till patient obeying commands) and extubation (stopping to propofol till removal of tracheal tube) was recorded. After satisfactory recovery, the patients were extubated, asked for VAS score (O time point) and shifted to the Neurosurgical Intensive care unit (NSICU). Another blood sample for S-100 B protein levels was collected at end of surgery.

On arrival in ICU, patient's pain intensity was assessed at 1 hour, 2 hours, 6 hours, 12 hours and 24 hrs after the operation by a single observer, who was blinded to the groups. Patient was explained to self-administer dose of fentanyl via PCA pump which was set at 0.5 μg/kg/bolus with lock out time interval of 10 minutes and 4 hour dose limit of 0.4 mg. No background infusion was given. If the patients VAS score was >40 despite administration of maximum set dose of fentanyl by PCA pump, injection ketorolac 30 mg intravenously was given as a rescue analgesic. Third sample for S-100 B level estimation was collected 24 hrs postoperatively. All patients received oxygen through face mask with a flow of 3 lit/min throughout the study period. Any side effects like sedation, respiratory depression, pruritus, nausea and vomiting were recorded. Any problems, if observed (excessive sedation, confusion, surgical complication) the PCA device was discontinued.

Data was analysed using software STATA 12.0 (College Station, Texas, USA). Data are expressed as mean (SD), number (%) and median (range) as appropriate. The baseline categorical and continuous variables were compared among the groups using Fisher exact test and one-way analysis of variance (ANOVA) test for independent variables respectively. The VAS scores and values of S-100 B were compared among the groups using generalized estimating equation analysis (GEES). Intraoperative variables like blood loss and urine output were compared among groups using Kruskall Wallis non-parametric ANOVA, since the data was not following normal distribution. A P value <0.05 was considered statistically significant.

Results

About sixty-eight patients were evaluated for eligibility, of which 45 patients fulfilled the inclusion criteria. They were assigned to three different groups of 15 each [Figure 1]. The characteristics of patients are described in Table 1 and these were comparable in all three groups. None of the patient had bradycardia severe enough to require atropine administration. None of the patient experienced any adverse hemodynamic effect intra-operatively secondary to lignocaine or magnesium. The intraoperative HR and MAP measured at baseline, induction, intubation, pin fixation, at one, two, three, four, five hours (hrs), extubation, and at time of shifting the patient from OT are shown graphically [Figures 2 and 3]. The amount of mephentermine and esmolol boluses used were also comparable among the groups. The amount of intraoperative fentanyl consumption, duration of anaesthesia and surgery were comparable among the groups [Table 1]. No adverse effects were observed in any group. Blood transfusion was required in 4 patients in group I, 2 patients in group II and one patient in group III. None of the patients had delayed recovery from anaesthesia after completion of surgery. One patient in saline group was not extubated because of massive blood loss intraoperatively. Another patient remained drowsy in postoperative period and he was reintubated when CT revealed pneumocephalus. One patient in magnesium group was electively ventilated in view of tense brain intraoperatively.

The mean VAS score was significantly less in group I and III [Group I (15.3 ± 6.0), Group II (24.8 ± 6.7), Group III (17.9 ± 7.6); ($P \leq 0.01$)]. The value of VAS at different time points is given in Table 2. The fentanyl

Table 1: Characteristics of patients and intraoperative variables [Mean±SD, N, Median (Range)]

	Group I (*n*=15)	Group II (*n*=15)	Group III (*n*=15)	*P*
Age (years)	37.3±12.5	37.4±9.9	34.7±10.2	0.75
Weight (kg)	64.4±11.5	65.2±13.4	66.5±11.6	0.89
Sex (M/F)	10/5	9/6	10/5	1.0
ASA (I/II)	2/13	1/14	1/14	1.0
Intravenous fluid (litres)	3.4±0.9	3.2±1.3	3.0±0.9	0.74
Blood loss (ml)	400 (100-2000)	300 (100-900)	350 (100-900)	0.53
Urine output (ml)	1500 (600-2500)	1200 (600-2300)	1600 (1000-2550)	0.25
Intraoperative fentanyl (μgm)	366±128.1	412.7±148.3	341±89.2	0.22
Duration of anaesthesia (min)	332±69.1	327.3±75.6	299.3±60.9	0.39
Duration of surgery (min)	258.3±59.5	250.7±99.2	229.7±62.3	0.42
Time to awakening (min)	13.9±6.4	12.2±6.4	12.3±4.7	0.66
Time to extubation (min)	15.5±5.9	14.5±6.8	14.6±5.6	0.68

M=Male, F=Female, ASA=American society of Anaesthesiologists, Group I- Lignocaine, Group II: Saline, Group III: Magnesium

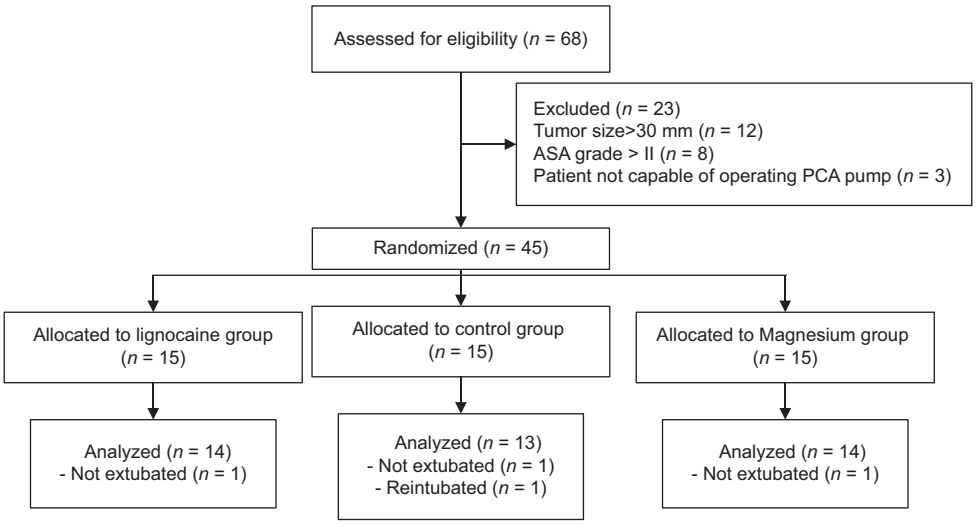

Figure 1: CONSORT flow diagram

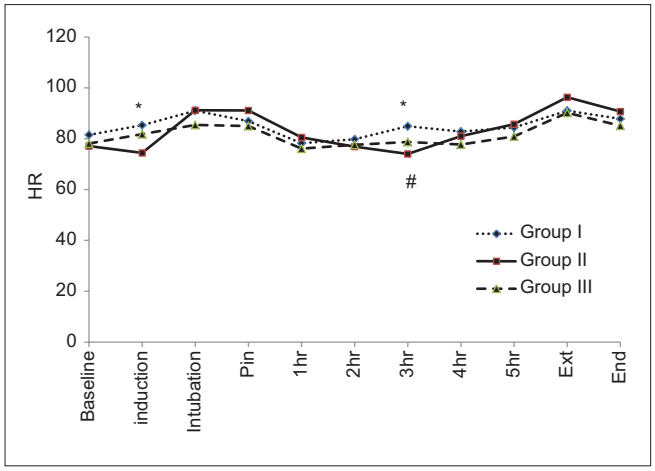

Figure 2: Intraoperative Heart rate (HR) at various time points

consumed in first postoperative 24 hours was significantly less in those patients who received lignocaine and magnesium [Group I (204.4 ± 136.4), Group II (383 ± 168.2), Group III (194 ± 148.9); (P = 0.01)]. None of the patients required administration of rescue analgesia in first 24 hours. The patients did not experience any side effect in postoperative period because of the study drugs. Value of S-100 B did not differ in the lignocaine and the saline group during the perioperative period. However, a significant decline was noted in the levels of S100 B in the magnesium group [Table 3].

Discussion

In this study, we found that intraoperative infusion of lignocaine and magnesium decreases the postoperative opioid requirement in patients undergoing craniotomy for excision of supratentorial tumours. It also resulted in lower VAS score over first 24 hours, implying better pain relief in patients. A significant decline was also noted in the levels of S100 B in the magnesium group as compared to the other two groups.

Perioperative lignocaine infusion significantly decreases pain after complex spine surgery.[5] We chose to administer

Table 2: Value of VAS over first 24 hours

VAS	0	1	2	3	4	5
Group I (n=14)	15±13.1*	14±2.48*	18.33±2.36*	18±1.95*	16±1.27	11.33±0.88*
Group II (n=13)	29.6±13.2	28.21±4.75	26.42±3.12	26.42±2.99	18.11±2.21	18.49±2.21
Group III (n=14)	18.6±18.7	18.57±4.88	19.28±2.79	20±3.68	13.92±2.29	15±2.65

*P-value ≤0.05, Group I Vs II Group I- Lignocaine, Group II: Saline, Group III: Magnesium, 0-Before shifting to ICU, 1-At 1 hrs, 2- At 2 hrs, 3-At 6 hrs, 4- At 12 hrs, 5-At 24 hrs postoperatively

Table 3: Value of S-100 B (picogram/ml) [Mean±SD, N]

S-100 B	Baseline	Immediate postoperative	24 hours postoperative
Group I	826.2±293*	701.7±295.9	860.7±214.7
Group II	993.1±113.8#	911.4±237.8	936.7±155.4#
Group III	851.4±240.8	773.4±258.5	708.8±281.0$

* Group I Vs II, #Group II Vs III, $Group I Vs III, ***P*** value ≤0.05.Group I- Lignocaine, Group II: Saline, Group III: Magnesium

these drugs only during intraoperative period because of the concern of interference in neurological state and to ensure preservation of protective upper airway reflexes during postoperative period. The dose of both lignocaine and magnesium employed in our study is similar to that used in earlier studies and has been found to be of devoid of any side effect.[9,10] None of our patients experienced any untoward side effect due to either drug. In a systematic review carried out by Barreveld and colleagues, in ten out of 16 trials, the pain relief lasted much longer than actual half-life of lignocaine.[11] The mechanisms other than sodium channel blockade, also play an important role in this. The pre-emptive analgesic effect by decreasing the pro-inflammatory effects (inhibition of intracellular G-protein signaling molecule) associated with surgery is an important mechanism. In patients undergoing abdominal surgery, lignocaine has shown to improve enhanced recovery after surgery outcomes (ERAS).[12] Hence, if true, lignocaine has a high potential in neurosurgical patients too. Similarly, magnesium has shown to have anti-nocciceptive effects in animal and human models of chronic pain. It reduces total anaesthetic and analgesic requirement as well as decreases postoperative pain.[4,13] While comparing these drugs, few authors have concluded that both reduce perioperative opioid requirement in patients, while others have found lignocaine infusion to be associated with better quality of postoperative recovery as compared to magnesium.[10,14,15]

The effect of drugs on hemodynamics is a major concern for any neuroanesthesiologist as hypotension has been clearly associated with poor outcome. There were no clinically significant variations in HR during bolus administration or any fluctuation attributable to study drugs which needed any intervention. Although, mean heart rate was lower in magnesium group at the time of intubation and skull pin insertion, but there was no significant difference

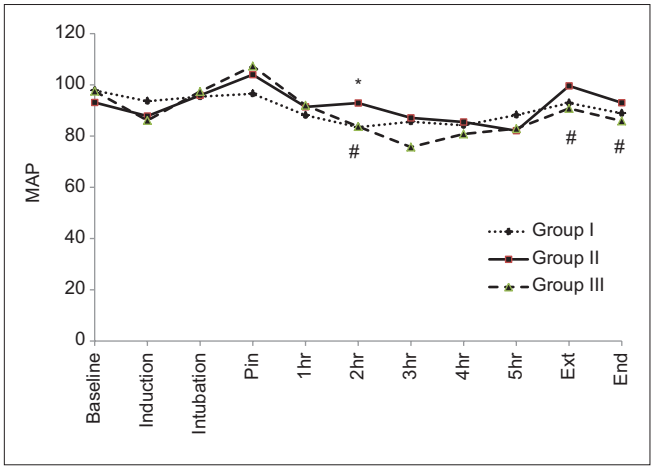

Figure 3: Intraoperative Mean Blood pressure (MAP) at various time points

among the three groups. Similarly, mean MAP was lower in lignocaine group at time of pin insertion but was statistically insignificant. There was a trend towards lower intraoperative MAP after one hour of surgery in magnesium group but was well within normal range only. This may be due to vasodilatory effect of magnesium. None of the patients in either group required discontinuation of study drug infusion. Ryu and co-workers found a significant effect of magnesium in blunting the pressor response associated with intubation.[9] We also found a similar trend but was insignificant among the three groups. At tracheal extubation, heart rate and MAP were lower in magnesium and lignocaine group as compared to the saline group. No adverse effect was observed in any of the three groups. There were no clinically significant variations in HR during bolus administration or any fluctuation attributable to study drugs which needed any intervention. None of the patients in either group required discontinuation of study drug infusion. We could not perform neuromuscular monitoring in all cases, but none of these patients showed undue prolongation of muscle relaxation. We titrated the propofol infusion on basis of BIS value but we did not calculate the total amount of anaesthetics or muscle relaxant used intraoperatively as it was not our objective. In our study, none of the patient had delayed recovery. Although cough reflexes were sluggish in lignocaine group, extubation was carried out as soon as patient was awake and responding to verbal commands. Moreover, we titrated propofol infusion to keep BIS 50-60 intraoperatively. This helped us extubate our patients early. The duration of surgery, anaesthesia, time

to awakening and extubation were similar among the three groups which coincides with the results of earlier studies.[9,14]

We found a significant difference in fentanyl requirement for first 24 hours among the three groups ($P = 0.01$), with less requirement in patients in magnesium and lignocaine groups which is similar to the results found in earlier studies.[10,14] In a recent Cochrane review, authors were unable to definitely conclude that perioperative lignocaine infusion has a beneficial impact on pain scores in early postoperative phase because of the inconsistency and imprecision in studies quality.[16]

We found significant difference in VAS scores when lignocaine was compared to the saline group. Even though VAS scores were lower in patients in both lignocaine and magnesium groups when compared to saline group, insignificant difference in VAS scores were observed when magnesium-saline group and lignocaine-magnesium group comparisons were made. However, it is a subjective measurement and should be considered along with assessment of fentanyl consumption. The amount of fentanyl requirement postoperatively was lower in both intervention groups when compared to saline group. However, it was comparable in both lignocaine and magnesium groups. Thus, the beneficial effect of lignocaine in reducing the fentanyl consumption as well as better VAS scores proves its analgesic effect. On the other hand, the opioid consumption is less in magnesium group but VAS scores are comparable to those in saline group. This supports that magnesium has an opioid sparing effect.

We also analyzed the effect of brain protective action of these drugs by measuring the plasma S-100 B levels. In contrast to the earlier studies, where levels of S100 B in newly diagnosed gliomas have been found to be 49-64 picogram/ml, in our patients the baseline value itself was found to range from 826-993 picogram/ml.[17] The plausible reason may be due to increased diagnosis to treatment time and advanced disease by the time patient reaches our referral centre. There was difference in the baseline S100 B value among the three groups, with highest levels noted in saline group. The value of S100 B in all the three groups was less than baseline at immediate postoperative period, but rose again at 24 hours postoperatively except in magnesium group. The value of S100B (24 hours postoperatively) in magnesium group when compared to saline and lignocaine group was found to be significantly lower. In this study, magnesium shows its potential neuroprotective effect, though its sustainability and effect on clinical outcome needs to be considered in further studies.

There are few limitations of our study. This was a preliminary study, so further large trials need to be carried out to confirm the results especially their role in enhanced recover after surgery and anaesthesia (ERAS) outcome in neurosurgical patients. We did not measure the blood levels of lignocaine and magnesium, though the doses administered were well within safe range, similar to those used in earlier studies.

To conclude, intraoperative infusion of lignocaine and magnesium decreases the postoperative opioid requirement in patients undergoing craniotomy for excision of supratentorial tumors. Lower VAS scores over first 24 hours implies better pain relief in these patients. Magnesium has a potential of providing neuroprotection which needs to be studied further.

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Conflicts of interest

There are no conflicts of interest.

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