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Effect of pre-emptive intravenous paracetamol, magnesium sulfate, and lignocaine on hemodynamic variables during perioperative period in pre-eclampsia patients scheduled for lower segment cesarean section under general anesthesia: A prospective randomized study

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ABSTRACT

Background: Hemodynamic alterations during general anesthesia with endotracheal intubation are due to stimulation of the sympathetic nervous system and catecholamine release. Therefore, it is important to attenuate these responses in pre-eclampsia patients who are already under stress. **Aims and Objectives:** The present study aimed to evaluate the combined efficacy of paracetamol, magnesium sulfate, and lignocaine in attenuating hemodynamic responses during intubation and perioperative period. **Materials and Methods:** Eighty ASA II pre-eclampsia patients were randomly divided into two groups. Group PLM received intravenous infusion of paracetamol (1 g) and magnesium sulfate (30 mg/kg) in 100 ml normal saline and IV bolus Inj. lignocaine (1.5 mg/kg) 15 min before induction. Group C received only IV infusion of 100 ml normal saline. Pulse rate (PR), blood pressure (BP), and oxygen saturation were measured at various time intervals up to 40 min of delivery of baby and in up to 240 min in post-operative period. Post-operative visual analog score (VAS) and the time for first rescue analgesia (TRA I) were recorded. **Results:** Demographic and baseline hemodynamic parameters were comparable in both groups (P>0.05). Changes in PR and BP during laryngoscopy, intubation, and perioperative period were significantly lesser in Group PLM as compared to Group C (P<0.05). The post-operative VAS score was significantly lower whereas TRA I was significantly longer in Group PLM than in Group C at all measuring times (P<0.05). **Conclusion:** Combination of paracetamol, magnesium sulfate, and lignocaine attenuates hemodynamic responses during laryngoscopy, intubation, and perioperative period along with prolonged post-operative analgesia in cesarean section under general anesthesia in pre-eclampsia patients.

Key words: Pre-eclampsia; Paracetamol; Lignocaine; Magnesium sulfate; Cesarean section; Laryngoscopy and intubation

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INTRODUCTION

Pre-eclampsia is now classified as hypertensive disease of pregnancy, a multisystem disease responsible for significant morbidity and mortality, complicating 5–8% of pregnancies.[1,2]

Hemodynamic alterations occurring during general anesthesia are due to stress and pain as a result of endotracheal intubation (ETI) and result in stimulation of sympathetic nervous system and catecholamine release, thus leading to increase in heart rate, arterial blood pressure (BP), pulmonary artery pressure, wedge capillary pressure,

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arrhythmias, and decrease uteroplacental blood flow thus leading to adverse neonatal outcomes.[3,4] Therefore, it is important to prevent or attenuate ETI responses during cesarean section done under genera anesthesia in pre-eclampsia patients. Many drugs such as lignocaine,[5] opioid,[6] nonnarcotic analgesics, magnesium sulfate,[7] esmolol,[5] nitroglycerine,[8] and gabapentin[9] have been used to blunt these responses during laryngoscopy and intubation.

Paracetamol has well-established safety profile as antipyretic and analgesic during all stages of pregnancy and labor.[10] Paracetamol selectively inhibits COX activities in the brain, which may contribute to its ability to treat fever and pain.[11] Magnesium has been used in anesthesia for wide range of applications including seizure prevention in pre-eclampsia, tocolysis, asthma management, and dysrhythmias.[12,13] Magnesium sulfate produces vasodilatation and causes fall in BP by diminishing sympathetic excitability of muscle cells. Magnesium has been an option for minimizing adverse cardiovascular responses during laryngoscopy and intubation due to its inhibiting effect on release of catecholamines from adrenergic nerve endings and adrenal medulla.[14]

Lignocaine is commonly used as an anti-arrhythmic drug in patients with ventricular ectopic due to membrane stabilizing action. IV lignocaine, when given before induction, has been proved to attenuate stress responses during laryngoscopy and intubation.[7,15]

Although paracetamol, magnesium sulfate, and lignocaine have been individually used for attenuation of hemodynamic changes during laryngoscopy and intubation, we could not find any single study using all three drugs simultaneously for this purpose. Hence, we planned to investigate the effect of pre-emptive intravenous paracetamol, magnesium sulfate, and lignocaine on hemodynamic variables during perioperative period in pre-eclampsia patients scheduled for lower segment cesarean section under general anesthesia.

Aims and objectives

This study aims to evaluate the combined efficacy of paracetamol, magnesium sulfate, and lignocaine in attenuating hemodynamic responses during intubation and perioperative period.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, informed written consent from 80 pre-eclampsia patients between 20 and 35 years of age (ASA Grade II), weighing between 40 and 60 kg, the present prospective, randomized, double-blind observational study was carried out between July 2020 and August 2021. Any uncooperative patient with refusal, history of any significant pulmonary, cardiovascular, endocrinal, neurological, hepatorenal, psychiatric or metabolic disease, and bleeding diathesis were excluded from the study. A detailed pre-operative assessment as per hospital protocol was carried out before surgery. Patients were interviewed for present or past medical and surgical problems. A routine physical examination along with relevant routine and special investigations such as urine (routine and microscopic), hemoglobin, total and differential leukocyte count, bleeding time and clotting time, liver function test, random blood sugar, and blood urea/serum creatinine were done. All the included 80 patients were randomly allocated into two groups by envelop method according to study drugs used as below:

Group PLM (n=40): Intravenous infusion of paracetamol (1 g) and Inj. magnesium sulfate (30 mg/kg) in 100 ml bottle along with Inj. lignocaine (1.5 mg/kg) IV bolus were given 15 min before induction.

Group C (n= 40): Intravenous infusion of 100 ml normal saline without any study drugs was given 15 min before induction.

All the patients were kept nil orally for at least 6 h before the procedure. On arrival of the patient in operation theater – a multipara monitor was attached to record hemodynamic parameters including basal pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), and oxygen saturation (SpO_2). An intravenous access was achieved with 18G cannula. All the patients were uniformly pre-medicated with IV Inj. glycopyrrolate 0.2 mg, Inj. ondansetron 4 mg, Inj. ranitidine 50 mg, and Inj. metoclopramide 10 mg followed by the study drugs 15 min before induction. Anesthetist and assistant on floor did not know the study drug infusion. After pre-oxygenation for 3 min, general anesthesia was induced with IV. Inj. thiopentone sodium 5 mg/kg. ETI was facilitated with Inj. succinylcholine 2 mg/kg and appropriate size endotracheal tube. Anesthesia was maintained on nitrous oxide+oxygen (66:33) along with intermittent isoflurane (0.5 MAC) to prevent awareness and non-depolarizing muscle relaxant Inj. atracurium on body weight basis for loading (0.5 mg/kg) and maintenance (0.1 mg/kg) doses. After delivery of baby, Inj. oxytocin 5 units in 100 ml normal saline and Inj. pentazocine 0.5 mg/kg I.V. were given. The anesthesia was reversed with Inj. neostigmine (0.05 mg/kg)+glycopyrrolate (0.004 mg/kg). Following parameters were observed and recorded for data collection and statistics:

1. Assessment of hemodynamic and respiratory parameters: PR, SBP, DBP, MAP, and SpO_2 were

recorded after intravenous infusion of study drugs, induction, laryngoscopy, intubation, after delivery of baby, and then at 10, 20, 30, and 40 min.

2. Assessment of post-operative hemodynamic and respiratory parameters: PR, SBP, DBP, MAP, and SpO_2 were recorded at 30 min up to 180 min and at 240 min postoperatively.
3. Assessment of visual analog score (VAS): All patients were assessed for pain by a VAS scale consisting of a 10 cm horizontal scale with gradations marked as 0 means no pain at all and 10 means worst pain imaginable as below:
   0 = No pain;
   1–3 = Mild pain;
   4–6 = Moderate pain;
   7–10 = Severe pain
4. Time for rescue analgesia: Once the VAS score >3 was reported by the patient, the time was recorded and rescue analgesia with inj. tramadol 2 mg/kg i.v. in 100 ml normal saline was given to relieve post-operative pain.
5. Perioperative and post-operative complications: Any side effect or complication due to the drugs or anesthetic technique were noted including hypotension, hypertension, bradycardia, tachycardia, respiratory depression, shivering, and post-operative nausea and vomiting (PONV). These were treated with appropriate drugs or other supports.

Statistical analysis

Evaluation of study data in electronic form required performing additional statistical analyses. Data were composed in a suitable spreadsheet, that is, Excel and SPSS. After compilation of data, it was analyzed statistically by SPSS software version 20.0. Statistical tests used were Student's t-test (paired and unpaired) and Chi-square test. Significance level will be 95% confidence level ($P<0.05$). Data were described as a frequency (percentage) distribution as well as in Mean±SD. Data were presented through suitable statistical graphs.

RESULTS

There was no statistically significant difference in terms of demographic parameters in both the groups ($P>0.05$) (Table 1).

There was no statistically significant difference in baseline intraoperative hemodynamic in both the groups ($P>0.05$). In Group PLM, PR and BP remained significantly stable as compared to Group C ($P<0.05$). In Group PLM, PR and BP showed a declining trend up to 40 min of the study period whereas in Group C, PR had initial rising trend and remained at higher value than the baseline values up to 40 min after baby delivery. BP in Group C remained higher or near base values throughout the intraoperative period (Table 2).

Table 1: Demographic profile of the study groups

Parameters	Group PLM (n=40)	Group C (n=40)	P value
Age (years)	25.73±4.37	26.93±4.65	0.238*
Weight (in kg)	52.33±5.05	50.85±6.36	0.254*
Duration of anesthesia (min)	51.35±4.21	50.4±4.35	0.324*

*P>0.05 – statistically insignificant, **P<0.05 – statistically significant

In post-operative period, change in pulse showed a rising trend in both the groups at 90 min but no statistically significant difference is observed in rest of the observation period (Table 3).

Time for first rescue analgesia was significantly longer in Group PLM (98.25±19.2 min) as compared to Group C (44.25±16.62 min) ($P<0.05$).

Post-operative complications in both the groups were comparable.

DISCUSSION

The main cause of hemodynamic instability during laryngoscopy and tracheal intubation is increased reflex sympathetic activity and release of adrenaline and noradrenaline.[16] This sudden increase in neurotransmitter activity leads to increase in BP, HR, and tachyarrhythmia. In normal patients, who do not have cardiovascular or cerebrovascular diseases, these responses can be tolerated, but in sick patients with CVD, such events may cause cerebral hemorrhage, left ventricular failure, and even myocardial ischemia.[17] Many studies have been done to prevent this rise in hemodynamic parameter using different stress blunting drugs.[18] Paracetamol, magnesium sulfate, and lignocaine are commonly available used drugs in operation room. These drugs have been used individually in attenuation of pressure response to laryngoscopy and intubation in intraoperative period. We did not find any study using all three drugs simultaneously for this purpose, hence with a hypothesis that summative effect of all three drugs will provide a stable hemodynamic variable and better control of post-operative pain.

In our study, demographic data were comparable in both groups ($P>0.05$). Majority of patients belonging to the age group of 20–30 years. The mean (±SD) weight (in kg) of

Table 2: Changes in Mean±SD PR, SBP, DBP, and MAP at different time intervals in intraoperative period between two study groups

S. No.	Time (min)	PR			SBP			DBP			MAP		
		Group PLM	Group C	P value	Group PLM	Group C	P value	Group PLM	Group C	P value	Group PLM	Group C	P value
1	B0	91.08±6.32	92.6±4.8	0.228*	151.2±7.14	151.45±7.78	0.881*	96.9±4.66	97.65±5.74	0.523*	115±4.53	115.58±4.23	0.553*
2	ASD	89.85±4.09	93.08±4.35	0.001**	148.85±6.42	151.6±6.31	0.057*	94.3±3.78	97.8±4.17	0.000**	112.48±3.85	115.73±3.19	0.000**
3	AI	82.25±6.05	95.45±4.77	0.000**	145.4±6.2	148.4±5.61	0.026**	91.2±4.1	95.05±3.9	0.000**	109.27±3.97	112.83±2.97	0.000**
4	AIT	82.75±4.85	101.95±3.7	0.000**	141.25±5.5	155.65±5.24	0.000**	86.35±3.65	101.7±4.21	0.000**	104.65±3.8	119.68±3.15	0.000**
5	ABD	83.15±5.32	101.75±3.3	0.000**	136.6±4.71	154.25±3.98	0.000**	86.75±4.98	100.2±4.41	0.000**	103.37±3.88	118.22±3.13	0.000**
6	ABD10	81.7±4.33	100.9±3.54	0.000**	129.2±7.16	150.5±3.92	0.000**	78.85±5.69	98.2±3.23	0.000**	95.63±4.98	115.63±2.52	0.000**
7	ABD20	81.15±3.95	99.95±3.4	0.000**	126.3±7.25	150.75±3.47	0.000**	79.6±4.62	97±3.07	0.000**	95.17±3.93	114.92±2.28	0.000**
8	ABD30	81.35±3.83	98.88±3.11	0.000**	128.65±7.46	148.4±3.4	0.000**	77±4.05	95.55±2.95	0.000**	94.22±3.51	113.17±2.17	0.000**
9	ABD40	81.25±3.59	98.6±3.27	0.000**	127.25±8.2	147.3±3.28	0.000**	77.95±6.33	94.1±2.64	0.000**	94.38±5.54	111.83±1.82	0.000**

*P>0.05 – statistically insignificant, ** *P*<0.05 – statistically significant, b0: Basal, asd: After study drug, Ai: After induction, Ait: After intubation, Abd: After baby delivery, abd10: After 10 min of baby delivery, abd20: After 20 min of baby delivery, abd30: After 30 min of baby delivery, abd40: After 40 min of baby delivery, PR: Pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean blood pressure

Table 3: Changes in Mean±SD PR, SBP, DBP, and MAP at different time intervals in post-operative period between two study groups.

S. No.	Time (MIN)	PR			SBP			DBP			MAP		
		Group PLM	Group C	p value	Group PLM	Group C	p value	Group PLM	Group C	p value	Group PLM	Group C	p value
1	P30	81.8±6.84	94.33±6.38	0.000**	129.45±5.36	146±5.78	0.000**	83.95±4.89	93.65±5.38	0.000**	99.12±3.6	111.1±4.47	0.000**
2	P60	81.9±6.85	93.05±4.3	0.000**	137±5.49	145.45±4.1	0.000**	84.35±4.1	93.05±4.2	0.000**	101.9±3.34	110.52±3.49	0.000**
3	P90	82.2±6.26	92.1±3.23	0.000**	140.4±6.21	141.5±3.5	0.332*	90±4.81	91.1±3.39	0.241*	106.8±4.04	107.9±2.81	0.161*
4	P120	89.65±6.12	88.95±3.33	0.527*	135.55±6.54	138.6±3.4	0.011**	92.15±5.75	88.45±3.58	0.001**	106.62±4.79	105.17±3	0.109*
5	P150	88.4±8.32	87.35±3.52	0.464*	130.15±5.57	135.25±4.07	0.000**	86.05±5.19	86.5±3.03	0.637*	100.75±4.26	102.75±2.77	0.015**
6	P180	83.8±6.21	86.2±2.59	0.027**	126.55±5.3	131.6±3.85	0.000**	82.1±4.53	84.55±3.59	0.009**	96.92±3.89	100.23±2.69	0.000**
7	P240	83.4±6.33	84.4±2.94	0.368*	125.1±4.15	129.55±3.15	0.000**	79.55±3.15	83.05±2.83	0.000**	94.73±2.65	98.55±2.1	0.000**

*P>0.05 – statistically insignificant, **P<0.05 – statistically significant, P30 – 30 min post-operative, P60 – 60 min post-operative, P90 – 90 min post-operative, P120 – 120 min post-operative, P150 – 150 min post-operative, P180 – 180 min post-operative, P240 – 240 min post-operative, PR: Pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean blood pressure patients in Group PLM and Group C was 52.33±5.05 kg and 50.85±6.36 kg, respectively. The mean (±SD) duration of anesthesia in Groups PLM and C was 51.35±4.21 min and 50.4±4.35 min, respectively.

Statistical analysis of PR between Group PLM and Group C showed a highly significant (P<0.00) decrease in PR in Group PLM as compared to Group C at the time of laryngoscopy and intubation and continued up to 40 min after delivery of baby. These finding confirms our hypothesis that when paracetamol, magnesium sulfate, and lignocaine are combined together, they showed better hemodynamic control. Ayatollahi et al.,[19] studied the effect of paracetamol (1 gm) on maternal hemodynamic variables, pain, and neonatal Apgar score. They observed that both PR and BP increased after laryngoscopy but HR returned to baseline or below baseline in paracetamol group whereas it remained above baseline in the control group. Bhalerao et al.,[20] compared the effect of magnesium sulfate and lignocaine in attenuating intubation response in hypertensive patients. They found that HR tends to decrease after induction with a brief increase after intubation in both the groups and but the difference was not statistically significant between the groups throughout the study period (P>0.05). They also observed that HR was lower in lignocaine group compared to group magnesium sulfate. Similarly, another study done by Padmawar and Patil[21] comparing magnesium sulfate (40 mg/kg) and lignocaine (1.5 mg/kg), noted that magnesium sulfate does not offer complete protection against increase in HR, the difference between both the groups in attenuating HR was significant at 1, 3, and 5 min interval but HR came to baseline toward 5 min after intubation in magnesium sulfate group but that was not the case with lignocaine group.

Paracetamol is an antipyretic and analgesic, has well-established safety profile during all stages of pregnancy and labor.[10,11] Magnesium sulfate is known to attenuate stress responses to ETI and to preserve favorable hemodynamic. It also produces vasodilatation and causes drop in BP by diminishing sympathetic excitability of muscle cells.[14,22,23] Lignocaine is a proven drug to attenuate stress responses during laryngoscopy and intubation when given before induction.[7,15]

Hemodynamic alterations occurring due to laryngoscopy and intubation causes increase in the BP but in our study, we found that combined effect of paracetamol, magnesium sulfate, and lignocaine effectively attenuate this response. In the PLM group, a highly significant reduction (P<0.001) was observed after giving study drug, and this fall continued till 40 min after the delivery of baby. Whereas in the control group, MAP decreased (P<0.001) at the time of induction but increased again after laryngoscopy (P<0.001). Jain and Khan[24] studied the effects of lignocaine on hemodynamic response during laryngoscopy and intubation. They observed significant rise in MAP with both the lignocaine and control groups (P<0.05), but the rise in lignocaine group was significantly less than in the control group. Similar results were observed by Gupta et al.,[16] Murthy and Kumar,[25] Bhalerao et al.,20 and Deka et al.,[26] observed a fall in SBP, DBP, and MAP from baseline after induction, laryngoscopy, and after 1 min of intubation in both the paracetamol and placebo groups but intergroup comparisons at these time points were statistically insignificant (P>0.05). However, the fall in HR was significant in the study group compared to the placebo group (P<0.0001). This shows that paracetamol failed to completely blunt all the cardiovascular responses to laryngoscopy and intubation. Therefore, in our study, we used combination of three drugs for better control.

Nooraei et al.,[27] and Sunil et al.,[28] compared role of IV magnesium sulfate and lignocaine in attenuating pressor responses. They observed that decrease in DBP, SBP, and MAP was more in magnesium sulfate group than the lignocaine group but the difference between the groups was statistically insignificant (P>0.05). Padmawar and Patil[21] revealed that magnesium sulfate provides fairly good and sustained control over hemodynamic responses to during laryngoscopy and intubation than lignocaine.

In our study, we observed, in the PLM group, post-operative hemodynamic parameters were more stable as compared to the control group. This might be the combined effect of paracetamol, magnesium sulfate, and lignocaine on post-operative analgesia. Kalani et al.,[29] compared analgesic effect of paracetamol and magnesium sulfate in recovery room and found no significant differences in HR and SBP (P>0.05).

Our study showed significantly prolonged analgesia with the PLM group (98.25±19.2 min vs. 44.25±16.62 min). After rescue analgesia, the patient remains pain free up to 240 min of study period in both the groups. However, VAS score was significantly lower in Group PLM as compared to the control group (P<0.05).

Murthy and Kumar[25], used lignocaine bolus as well as infusion and found an increase in mean pain-free period postoperatively. Ayatollahi et al.,[19] studied the effect of paracetamol (1 gm) on post-operative pain, the mean VAS score was significantly lower in paracetamol group compared to placebo group till 6 h after surgery. Thus, the time for first dose of analgesic was more in paracetamol group. Altiparmak et al.,[30] did a study to see the effect of magnesium sulfate on post-operative analgesia and found significantly lower VAS score in magnesium group during the study period.

Pre-operative iv lignocaine infusion decreases anesthetic drug requirement during intraoperative period. It also decreases requirement of post-operative analgesics and pain score.[25] Suppression of neuronal excitability in dorsal horn neurons, depression in spike activity, amplitude, and conduction time in both myelinated A and unmyelinated C fibers, and decrease in the neural response to postoperative pain by blockade or inhibition of nerve conduction may offer the analgesic action of iv lignocaine.[31,32] Paracetamol belongs to an aniline analgesic class of drugs and is an active metabolite of phenacetin, has a well-established safety and analgesic profile. The main mechanism of action is inhibition of cyclo-oxygenase enzyme, which is responsible for the production of prostaglandins, an important mediator of inflammation and pain.[32] According to Kalani et al.,[29] magnesium is a natural blocker of calcium channel with analgesic effects. Furthermore, magnesium sulfate suppresses the passage of electrical currents through membrane by suppressing the NMDA receptor. It is effective in preventing the emergence of pain and in its control. Paracetamol, magnesium sulfate, and lignocaine alone provide inadequate suppression of pressor response and post-operative analgesia. We used a combination of all the three drugs for summative effect on these parameters.

Kalani et al.,[29] in their study when comparing analgesic effect of paracetamol and magnesium sulfate during surgeries, observed nausea in six patients in the control, in two patients in the paracetamol, and in five patients in the magnesium sulfate groups. The groups were not significantly different with respect to nausea in the recovery room ($P>0.05$). Valeshabad et al.,[33] observed the incident rates of hypertension, hypotension, and tachycardia were significantly ($P<0.05$) lower in group paracetamol as compared to group lignocaine. Flather M et al.,[22]when seeing the effect of intraoperative magnesium sulfate infusion observed PONV and shivering in four patients in the control group and three patients in magnesium sulfate group. Similarly, Padmawar and Patil[21] did a comparative study of lignocaine and magnesium sulfate for attenuation of stress responses to laryngoscopy and intubation found no incidence of nausea, vomiting, hypertension, hypotension, tachycardia, and bradycardia among the study groups. Our study showed that combination of paracetamol, magnesium sulfate, and lignocaine has lesser complication in comparison to the control group.

Limitations of the study

We studied only ASA II patients undergoing lower segment caesarean section surgery and Therefore, cannot be generalized to patients undergoing different surgical procedures. The safety profile of the drug combinations in patients with co-morbidities and critically ill patients were not studied. As we did not monitor TOF sequence hence factors other than laryngoscopy like depth of anaesthesia or adequacy of muscle relaxation which might affect haemodynamic changes were not monitored in our study.

CONCLUSION

Based on the results of present clinical comparative study, we conclude that combination of paracetamol, magnesium sulfate, and lignocaine is effective in attenuating hemodynamic responses to laryngoscopy and intubation. This combination also provides better hemodynamic stability during intraoperative and post-operative period in pre-eclampsia patients scheduled for lower segment cesarean section under general anesthesia. When given together, paracetamol, magnesium sulfate, and lignocaine provide effective and prolonged post-operative analgesia.

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