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EFFECT OF MATERNAL HYPERURICEMIA ON POST-SPINAL HYPOTENSION IN PREECLAMPTIC PARTURIENTS UNDERGOING ELECTIVE CESAREAN DELIVERY: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Serum Uric acid (UA) is a marker of oxidative stress in preeclampsia. Hyperuricemia has been shown to be associated with impaired vascular relaxation in some retrospective studies. Elevated uric acid is also an independent predictor of hypertension. This study is designed to study the association between elevated serum uric acid levels and post spinal hypotension in pregnancy induced hypertension patients undergoing elective caesarean delivery under spinal anesthesia , as measured by requirement of vasopressors. **MATERIALS AND METHODS:** 204 patients with pregnancy induced hypertension scheduled for elective caesarean section under spinal anesthesia were included in the study. Demographic data, anesthetic management and peripartum course were recorded. Serum uric levels were measured on arrival to operation theatre. Doses of vasopressor agents required after spinal anesthesia was recorded. The association between serum uric acid level and requirement of vasopressor was studied. Data was analysed using students t test and chi-square test. P-value<0.05 was considered significant. **RESULTS AND OBSERVATIONS:** Requirement of vasopressors was lower in patients with high serum uric acid levels than those with lower serum uric acid levels. Results were similar with both phenylephrine and ephedrine. The difference in vasopressor requirement was statistically significant.(p-value<0.05) **CONCLUSION:** Elevated serum uric acid levels are inversely related to development of post spinal hypotension and requirement of vasopressors in preeclamptic patients undergoing cesarean section under spinal anesthesia.

KEYWORD

Serum uric acid, Post spinal hypotension, Preeclampsia, Vasopressors,

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INTRODUCTION:

Pregnancy is a physiological stress in which many changes occur in the milieuinterior of the body, more and more stress is being laid on the biochemical changes, which occur in the blood during normal pregnancy becomes exaggerated in complications of pregnancy like pre-eclampsia.[1] Oxidative stress increases during pre-eclampsia and results in increased production of lipid peroxides, reactive oxygen species and superoxide anion radicals to cause endothelial injury and dysfunction, platelet and neutrophil activation[2-3]. Uric acid (UA) is a marker of oxidative stress. Recent retrospective reports have associated hyperuricemia with decrease in vascular relaxation. Association between elevated serum uric acid (UA) and preeclampsia has been attributed to renal dysfunction and the degradation of purines from maternal, fetal or placental tissues Increasing evidence suggests that the rise in uric acid in pre-eclampsia is not merely a nonspecific reflection of kidney damage, but a sign of antioxidative response, possibly related to the pathogenesis of pre-eclampsia[4]. The enzyme responsible for metabolizing purines to UA is xanthine oxidase/ dehyd rogenase (XO), which produces reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, as by-products. Oxidative stress is considered an essential contributor to the development and maintenance of preeclampsia,[5]and serum UA has subsequently been proposed as an appropriate marker for the severity of this stress[6,7]. An elevated UA has been observed to be an independent predictor for the development of hypertension.[8,9] During pregnancy, oxidative stress may be responsible for the impaired relaxation of vascular smooth muscle that results in hypertension, a signature feature of preeclampsia.[10] The hypertension associated with preeclampsia can exhibit significant resistance to multimodal antihypertensive therapy; even the administration of spinal anaesthesia results in less hypotension in preeclamptic than in healthy parturients.[11] Based on these observations, we devised this study to study the association between elevated serum uric acid levels and post spinal hypotension in pregnancy induced hypertension patients undergoing caesarean delivery under spinal anaesthesia.

MATERIALS AND METHODS:

This prospective observational clinical study was conducted in the department of Anaesthesiology and critical care, in a tertiary care institute. The study was conducted after approval by the Institutional Ethical Committee and an informed written consent was obtained from all the patients for participation in this study. Preanaesthetic evaluation was done for all patients participating in this study. A totalof 200 patients with documented pregnancy induced hypertension were enrolled for the study.

Patients with the following parameters were excluded from the study:

1. Patient refusal

2. Raised intracranial tension
3. Bleeding disorders or anticoagulation therapy 4.Infection at local site
5. Hypersensitivity to drugs given to these patients
6. Deformity of lumbar spine
7. Hyperuricemic patients
8. Patients on drug therapy for hyperuricemia
9. Uncontrolled BP at the time of study
10. End organ damage secondary to PIH
11. Preeclampsia or eclampsia at the time of study
12. Patients requiring general anesthesia for LSCS
13. Patients not having properly maintained antenatal medical records

All the patients were premedicated with oral ranitidine 150mg a night before surgery. On arrival to operation theatre, intravenous cannula was secured and blood sample for estimation of serum uric acid level was taken from all the patients. Standard anaesthetic monitoring viz electrocardiogram, non invasive blood pressure, pulse oximetry shall be instituted before taking the sample**.** All the baseline parameters (heart rate, blood pressure and oxygen saturation) will be recorded prior to spinal anesthesia and at 5 minute intervals till the end of surgery. All the patients will be preloaded with lactated ringers solution 10 ml/kg bodyweight prior to spinal anaesthesia. The procedure will be carried out in lateral decubitus or sitting position with 27 gauge spinal needle. Proper position of spinal needle in sub-arachnoid space will be confirmed by free flow of cerebrospinal fluid. Heavy Bupivacaine 12.5mg **(2.5ml)** with fentanyl 25mcg **(0.5ml)** was administered into the subarachnoid space **(total 3ml)**.

Sensory block was checked with response to ice packs with target highest sensory level to be achieved at T4 level.
Motor blockade: This will be assessed by Modified Bromage Scale as under:Grade 0:No Paralysis.

Grade 1:Unable to raise extended leg against gravity but able to flex knee. Grade 2: unable to flex knees but able to flex ankle.
Grade 3:unable to flex ankle and foot.

Surgery was started after confirmation of sensory block and motor block. Injection oxytocin 5U i.v. bolus followed by 15U continuous infusion in normal saline at the rate of 5u/h was given to all patients. Additional oxytocin and prostaglandin E1 were given as rescue uterotonic drugs in case of inadequate uterine contraction with intial dose of oxytocin in both groups. Injection methyl ergotomine as uterotonic drug **was strictly avoided in all patients**.

Hypotension was defined as drop of more than 20% in basal mean arterial blood pressure or systolic blood pressure less than 100mmHg or diastolic blood pressure less than 60mm Hg. Hypotension was treated with bolus doses of injection ephedrine 6 miligrams in patients with heart rate of less than 60bpm and with injection phenylepherine bolus doses of 50mcg in patients with heart rate more than 100bpm respectively. Total dose of vasopressor agents required and the total number of doses of vasopressor agents required in each patient were recorded for statistical analysis. Oxygen supplementation was provided in case of respiratory depression that is SPO2 < 90% and respiratory rate <8.

Collection of blood sample and administration of vasopressor agents was performed by an anesthesiologist not participating in the study. These were in coded form that were decoded at the end of study. Any untoward incident or side effect like nausea, vomiting, hypotension, respiratory depression, drowsiness, etc. were recorded.

All statistical analysis was done using SPSS software. Discrete variables will be expressed as counts i.e as percentage (%), and continuous variables as mean +/- standard deviation. Analysis was done using student t-test and p value of less than 0.05 was considered significant.

RESULTS AND OBSERVATIONS:

A total of 204 patients with documented pregnancy induced hypertensionscheduled for elective cesarean section under spinal anaesthesia were enrolled for the study. Minimum age and maximum age of 20 years (16) and 35 years (16) respectively most of the patients (80) enrolled in the study were observed in the age group 28-30 years. of the 204 enrolled PIH patients in the study 120 (58.8%) patients had significantly higher serum uric acid levels (>5.7).

Out of the 204 enrolled patients in the study, 140 patients had a mean serum uric acid level of 6.3mg/dl and they didn't require any dose of ephedrine whereas 64 patients with an average serum uric acid level of 4.9mg/dl required 1-2 doses of ephedrine.48 patients who required one dose of ephedrine has a mean serum uric acid level of 4.655 mg/dl. The difference in serum uric acid level was statistically highly significant when compared to patients who did not require any ephedrine (p- value <0.001). Serum uric acid was also lower in patients who received two doses of ephedrine than those who did not require any ephedrine (5.725 mg/dl vs 6.368 mg/dl respectively). However the difference was not statistically significant (p-value 0.063). It was also observed that of the 204 enrolled patients 124 patients with an average serum uric acid level of 6.8 didn't require any dose of phenyepherine, whereas 80 patients with an average serum uric acid level 4.5 required 1-3 doses of phenylepherine. The difference was statistically significant (p value <0.001)

Out of the 204 enrolled patients 124 patients with an average serum uric acid level of 6.8mg/dl didn't require any dose of phenyepherine whereas 80 patients with an average serum uric acid level 4.5 mg/dl required 1-3 doses of phenylepherine.40 patients who required only one dose of phenylephrine has a mean serum uric acid level of 4.65mg/dl. The difference was statistically significant when compared to patients who did not require phenylephrine (p- value <0.001).16 patients requiring two doses of phenylephrine had a mean serum uric acid level of 4.725mg/dl which was lower than those patients who did not require any dose of phenylephrine. Again the difference was statistically significant (p-value 0.001).24 patients who required 3 doses of phenylephrine also had mean serum uric acid levels lower than those who did not require phenylephrine (4.066mg/dl vs 6.833mg/dl respectively). The difference was statistically highly significant. (p- value <0.001)

Table 1:Showing Age distribution of patients taken for the study

AGE	FREQUENCY	PERCENT
20	16	7.8
22	16	7.8
24	8	3.9
25	20	9.8
26	8	3.9
28	24	11.8
29	40	19.6
30	16	7.8
31	16	7.8
32	24	11.8
35	16	7.8
Total	**204**	**100.0**

Table 2: Showing the number of PIH patients on medication.

DRUG	FREQUENCY	PERCENT
LABETALOL	164	80.4
100		
NIL	40	19.6
Total	**204**	**100.0**

Table 3: Showing the serum uric acid (mg/dl) correlation with pregnancy induced hypertension.

SERUM URIC ACID (mg/dl)	FREQUENCY	PERCENT
<=5.7	84	41.2
>5.7	120	58.8
Total	204	100.0

Table 4: Showing the relation between level of Serum Uric Acid and Ephedrine in PIH patients undergoing caesarian under spinal anesthesia.

EPHEDRINE		N	Mean	Std. Deviation	P value
SERUM URIC ACID (mg/dl)	NO	140	6.3680	1.69435	<0.001
	YES	64	4.9225	1.52683	

Table 5: Showing the relation between level of Serum Uric Acid and dose of Ephedrine in PIH patients undergoing caesarian under spinal anesthesia.

EPHEDRINE	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	P-value
				Lower Bound	Upper Bound			
No dose	140	6.368	1.69435	6.0849	6.6511	2.70	8.20	
1 dose	48	4.655	1.54133	4.2074	5.1026	2.60	7.90	<0.001
2 doses	16	5.725	1.19638	5.0875	6.3625	4.90	7.70	0.063
Total	204	5.914	1.77237	5.6698	6.1592	2.60	8.20	

Table 6: Showing the relation between level of Serum Uric Acid and Phenylephrine in PIH patients undergoing caesarian under spinal anesthesia.

PHENYLEPHRINE		N	Mean	Std. Deviation	P value
SERUM URIC ACID (mg/dl)	NO	140	6.3680	1.69435	<0.001
	YES	64	4.9225	1.52683	

Table 7: Showing the relation between level of Serum Uric Acid and dose ofPhenylephrine in PIH patients undergoing caesarian under spinal anesthesia.

PHENYLEPHRINE	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	P value
				Lower Bound	Upper Bound			
No	124	6.833	1.174	6.624	7.0422	4.10	8.20	<0.0
1dose	40	4.650	1.821	4.067	5.2325	2.60	7.90	01
2doses	16	4.725	2.063	3.625	5.8246	2.90	7.70	0.001
3 doses	24	4.066	0.268	3.953	4.1799	3.70	4.30	<0.0
Total	204	5.914	1.772	5.669	6.1592	2.60	8.20	01

Table 8: Showing frequency of side effects.

SIDE EFFECT	PRESENT	NUMBER	PERCENTAGE
HYPOTENSION	YES	88	43.1
	NO	116	56.9
NAUSEA	YES	16	7.8
	NO	188	92.2
VOMITING	YES	0	0
	NO	204	100
BRADYCARDIA	YES	8	3.9
	NO	196	96.1

DISCUSSION:

In our study we observed that an elevated serum uric acid level in pregnancy induced hypertension patients undergoing cesarean delivery under spinal anaesthesia was associated with lower vasopressor use. These findings are consistent with the observation that the incidence of spinal anesthesia-induced hypotension during pregnancy is significantly lower in patients with severe preeclampsia when compared to healthy, normotensive women.[11,12] A prospective cohort study controlling for neonatal weight, observed a significantly lower incidence of hypotension (24.4% vs. 40.8%,) and vasopressor requirements (ephedrine 9.8 ± vs. 15.8 ± 6.2 mg) after spinal anesthesia for cesarean delivery in patients with severe preeclampsia compared to healthy parturients.[11] These results were confirmed in another study where the range in vasopressor use, when converted into phenylephrine equivalents, similar to our study.[13]

The mechanism by which an elevation in serum UA can serve as a marker for hypertension appears to be related to the synthesis of endothelial nitric oxide.[14,15] The addition of plasma from women with preeclampsia to biopsy samples from women without preeclampsia can inhibit normal uterine vasorelaxation.[16] Theresulting vasoconstriction is reversed with the normalization of serum UA.[17] Allopurinol, a XO inhibitor which leads to a reduction in serum UA, has been used successfully in the treatment of hypertension.[18] By contrast, a small study found no correlation between serum UA levels and vessel relaxation or the effect of plasma from preeclamptic patients on in vitro endothelial function, however, this study was likely underpowered.[19] Hypertensive parturients have elevated concentrations of circulating vasopressors, such as thromboxane and endothelin, with parallel decreases in vasodilators such as prostacyclin.[20,21] The maternal vasculature of hypertensive parturients also exhibits increased sensitivity to pressor agents.[22] It is proposed that this is in part due to reduced availability of nitric oxide secondary to the endothelial dysfunction.[23] Elevated uric acid concentration could participate in reduced production of nitric oxide (NO) and may in part explain the altered endothelial contribution to vascular tone in hypertensive parturients.

A trend towards lower vasopressor use after spinal anaesthesia was observed with increasing serum uric acid. The results were similar with both ephedrine and phenylephrine. Our results are similar to study done by Kochapava et al[24] who studied the relation between elevated serum uric acid level and vasopressor use in patients undergoing neuraxial anaesthesia for caesarean delivery and found that elevated serum uric acid in parturients is associated with decreased use of post spinal vasopressors.[24]

The results of our study are also the same as the study conducted by Bhatia N et al.[25] They studied the effect of maternal hyperuricemia on post-spinal hypotension in normotensive parturients undergoing non elective caesarean delivery in a prospective observational study and observed that elevated serum uric acid levels were associated with lower incidence of post spinal hypotension and reduced need of vasopressors to maintain blood pressure within a normal range.[25]

LIMITATIONS:

Serum UA levels can increase with food intake, which was not controlled in our study. The serum UA levels obtained in the postoperative period may be influenced by the dilutional effects of intravenous fluids administered during the cesarean delivery or by resolution of the hypertensive disorder. To avoid this, all samples were taken preoperatively before instituting fluid loading.

CONCLUSION:

Elevated serum uric acid levels were inversely related to development of hypotension and requirement of vasopressor to maintain blood pressure within normal range in preeclamptic parturients undergoing spinal anesthesia for caesarean delivery. From the study, we conclude that serum uric levels are increased in patients with pregnancy induced hypertension, and in addition to serve as a marker of disease elevated serum can predict the development of hypotension after spinal anesthesia for elective caesarean section in such patients.

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