VOLUME - 9, ISSUE - 8, August - 2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Anaesthesiology

SERUM URIC ACID AS A MARKER OF PREGNANCY INDUCED HYPERTENSION AND ITS ASSOCIATION WITH UTERINE ATONY IN PRE-ECLAMPTIC PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANESTHESIA.

Sheikh Irshad Ahmad	Additional professor, Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.
Shaista Yaqoob	Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.
Tantry Tariq Gani*	Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India. *Corresponding Author
Tanveera Gani	Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.
Syed Yusra Imtiyaz	Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India.

ABSTRACT **Introduction:** Serum uric acid is a marker for oxidative stress in preeclampsia. Recent retrospective studies have associated hyperuricemia with decreased uterine contractility Because oxidative stress can result in diminished uterine contractility and impaired vascular relaxation. The study was aimed to study association of elevated serum uric acid level in women undergoing neuraxial anesthesia for cesarean delivery with greater uterine atony, as measured by supplemental uterotonic agent use. **Methods:** 204 patients with pregnancy induced hypertension scheduled for elective caesarean section under spinal anesthesia were included in the study. Demographic data, medical and obstetric history, anesthetic management and peripartum course were recorded. Serum uric levels were measured within 24 hours of caesarean delivery. Dose of uterotonic agents received was recorded in all patients. The association between serum uric acid level and uterotonic agent use was studied. Data was analysed using students t test and chi-square test. **Results:** 72 patients required 20 IU oxytocin has lower serum acid levels (4.6444±1.74169) than 132 patients who required >20 IU of oxytocin(6.6073±1.36146) (p value <0.001).In patients requiring more than 20 IU oxytocin, patients requiring 30 IU of oxytocin had higher serum uric acid levels than those requiring 25 IU of oxytocin. The difference in serum uric acid was statistically highly significant.(p-value < 0.001) **Conclusion:** Elevated serum uric acid in parturients undergoing cesarean delivery with neuraxial anesthesia was associated with increased use of supplemental uterotonic agents.

KEYWORDS : pre-eclampsia, uric acid levels, oxidative stress, uterotonic agents.

INTRODUCTION:

Preeclampsia is a common disorder of human pregnancy and a major cause of worldwide pregnancy-related maternal and neonatal morbidity and mortality. Oxidative stress, angiogenic imbalance, placental ischemia and an inflammatory response have been proposed to play role in the pathogenesis of the disease.[1] Hyperuricemia is a key biochemical feature in preeclampsia with elevated levels of uric acid being diagnosed as early as the 10th week of gestation.[2] Elevated uric acid concentrations were first noted in pre-eclamptic women in the late 1800s. Since that time numerous reports have demonstrated a relationship between uric acid concentrations and severity of disease. [3,4] Increasing evidence suggests that an elevated serum uric acid in pregnancy may not only be a valuable biomarker of preeclampsia but may also have a contributory role in the pathogenesis of maternal and fetal manifestations.[5] Elevated uric acid concentration could participate in reduced production of NO and may in part explain the altered endothelial contribution to vascular tone in preeclamptic women.[6] In-vitro culture studies and hyperuricemic animal models demonstrate several pathogenic effects of uric acid, including pro-inflammatory effects, stimulation of smooth muscle cell proliferation, inhibition of endothelial cell proliferation and migration, promotion of endothelial dysfunction and damage. These insults all play pivotal roles in the pathophysiology of preeclampsia.[7]

Thus serum uric acid is a marker for oxidative stress in preeclampsia. Because oxidative stress can result in diminished uterine contractility and impaired vascular relaxation, an elevated serum uric acid level in women undergoing neuraxial anesthesia for cesarean delivery would be associated with greater uterine atony, as measured by supplemental uterotonic agent use.

The purpose of this study was to correlate the level of serum uric acid with requirement of vasopressors and ionotropes as literature for this is scarce

MATERIALS AND METHODS:

This prospective observational clinical study was conducted in the department of Anaesthesiology and critical care, Sheri Kashmir Institute of Medical Sciences, Kashmir, India from september 2017 to August 2019. 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 total of 204 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 150 mg 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 was instituted before taking the sample. All the baseline parameters including heart rate(HR-bpm), blood pressure(BP-mm Hg) and oxygen saturation of haemoglobin (SPO_2%) were recorded prior to spinal anesthesia and at 5 minute intervals till the end of surgery. All the patients were preloaded with lactated Ringer solution 10 ml/kg bodyweight prior to spinal anesthesia. The procedure was carried out in lateral decubitus or sitting position with 27 gauge spinal needle. Proper position of spinal needle in sub-arachnoid space was confirmed by free flow of cerebrospinal fluid. Hyperbaric 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 was 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 5 U i.v. bolus followed by 25 U continuous infusion in normal saline at the rate of 5 U/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. Total consumption of these uterotonic drugs was recorded in each patient for statistical analysis. Hypotension was defined as drop of more than 20% in basal mean arterial blood pressure or systolic blood pressure less than 100 mmHg or diastolic blood pressure less than 60 mm Hg. Hypotension was treated with bolus doses of injection ephedrine 6 mg in patients with heart rate of less than 60 bpm and with injection phenylepherine bolus doses of 50 mcg in patients with heart rate more than 100 bpm respectively. Oxygen supplementation was provided in case of respiratory depression that is SPO2 < 90% and respiratory rate <8.

Collection of blood sample and administration of uterotonic 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 like nausea, vomiting, hypotension, respiratory depression, drowsiness, etc. were recorded.

Statistical Analysis:

All statistical analysis was done using SPSS software. Discrete variables were 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 pregnancy induced hypertension undergoing caesarean delivery under spinal anaesthesia were enrolled in this study. Most of the patients(80) enrolled in the study were observed of the age group 28-30 years with a minimum age and maximum age of 20 years (16) and 35 years (16) respectively. [Table 1].

Table 1: Showing Age (in Years) Distribution Of Patients Taken For The Study

AGE (years)	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

Of the 204 patients enrolled in the study 164 were on medication (labetalol) for pregnancy induced hypertension. [Table 2].

Table 2: Showing The Number Of Pregnancy Induced Hypertension Patients On Medication.

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

Serum uric acid had a mean level of 5.9 (higher than upper limit of normal) with a minimum and maximum value of 2.6 and 8.20 respectively. Serum uric acid levels showed an average of 5.9 with a minimum and maximum level of 2.6 and 8.2 respectively. It was observed that of the 204 enrolled PIH patients in the study 120(58.8%) patients had significantly higher serum uric acid levels (>5.7). [Table 3].

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

In the study it was observed that the around 72 patients with an average serum uric acid level of 4.6 mg/dl required lower doses of uterotonic drugs (oxytocin) whereas 132 patients with a mean serum uric acid of 6.6mg/dl required higher and repeated doses of uterotonic drugs. The difference was statistically significant.(p value <0.001) [Table 4 a].

Table 4 (a) & (b): Showing the relation between level of serum uric acid (mg/dl) and oxytocin {International Units (IU)} in pregnancy induced hypertension patients undergoing caesarian under spinal anesthesia.

OXYTOCIN	N	Mean Serum Uric Acid (mg/dl)	Std. Deviation	P value
20IU	72	4.6444	1.74169	<0.001
>20IU	132	6.6073	1.36146	

OXYTOCIN	n	Mean (UA) (mg/dl)	Std. Deviation	95% Confidence Interval for Mean		Min.	Max.	P value
				Lower Bound	Upper Bound			
20IU	72	4.6444	1.741	4.235	5.053	2.60	8.20	
25IU	76	6.8537	1.033	6.617	7.089	5.00	8.20	<0.001
30IU	56	6.2729	1.661	5.827	6.717	2.70	7.64	<0.001
Total	204	5.9145	1.772	5.669	6.159	2.60	8.20	

72 patients required 20 IU oxytocin had a mean serum uric acid of 4.6 mg/dl.76 patients who required 25 IU of oxytocin had higher mean serum uric acid of 6.85mg/dl. The difference was statistically significant (p- value < 0.001). Also 56 patients required 30 IU of oxytocin. Their mean serum uric acid was 6.27 mg/dl which was higher than those who required only 20 IU of oxytocin. The difference was statistically significant (p value<0.001) [Table 4 b].

Out of the 204 patients enrolled, 88 patients (43.1%) developed hypotension, 16 patients (7.8%) developed nausea and 8 patients (3.9%) developed bradycardia (TABLE 5) intraoperatively. No incidence of respiratory depression was noted in any patient in our study.

Table 5: 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:

Uric acid is a product of purine degradation .The enzyme responsible for metabolizing purines to UA (uric acid) is xanthine oxidase / dehydrogenase (XO), which produces reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, as by-products. Uric acid is a plasma antioxidant capable of scavenging superoxide, hydroxyl radical and singlet oxygen. [8] Conversely, uric acid itself can become a pro-oxidant (urate radical) in a setting of compromised antioxidant availability, particularly reduced ascorbate availability [9,10] Oxidative stress is considered an essential contributor to the development and maintenance of preeclampsia, and serum UA has subsequently been proposed as an appropriate marker for the severity of this stress.[11] We conducted this study with the aim of studying the effect of elevated uric acid concentration on uterine tone and use of uterotonic agents in pre-eclamptic patients undergoing elective caesarean section under spinal anesthesia.

204 patients with pregnancy induced hypertension scheduled for elective caesarean delivery under spinal anesthesia were included in this study. The association between serum uric acid levels and dose of uterotonic agents received was studied. The results of our study suggest that pregnant women with pregnancy induced hypertension with an elevated serum uric acid require additional supplemental uterotonic agents following cesarean delivery under spinal anesthesia. The observation that elevated serum Uric Acid can serve as a marker of impaired uterine tone during cesarean delivery and the need for supplemental uterotonic agents is consistent with the influence oxidative stress and Reactive Oxygen Species have on cardiac myocytes. Elevated UA and Reactive oxygen species (ROS) have been associated with depressed myocyte contractility, mechanoenergetic uncoupling (i.e., the mechanical efficiency of contractions for a given amount of oxygen consumed),[12 13,] and apoptosis.[14] Furthermore, inhibition of XO increases myocardial contractility at rest [12] and exercise.[15,16]

In uterine biopsies obtained from women undergoing caesarean deliveries reactive oxygen species have been observed to significantly impair myometrial contractility, particularly with the addition of xanthine oxidase [17]. Within clinical obstretic care, factors predisposing to uterine atony which also have association with oxidative stress include prolonged labour, hypertensive diseases of pregnancy, chorioamnionitis, multiple gestations and retained placenta.[18-20] In pregnant human uterus xanthine oxidase produced reactive oxygen species have been demonstrated to significantly impair the contractility of non-labouring myometrium retrieved at caesarean delivery.[17]

Our findings are consistent with the results obtained in a study by Kovacheva VP et al who observed that increased serum uric acid correlated positively with preeclampsia and the need for supplemental uterotonic agents.[21] Our study results also correlate with the study conducted by Bhatia N et al who studied the association between serum uric acid levels and impaired uterine contractility in non elective caesarean deliveries in normotensive parturients and observed that greater percentage of patients who required supplemental uterotonic agents had hyperuricemia, although the results were not statistically significant.[22]

There are several limitations to our study. First serum uric acid levels can change with diet and diet was not controlled in our study. Serum UA levels may be affected by a multitude of genetic, environmental, and other unknown factors. Dilutional effect of intravenous fluids given during surgery can result in lowering of serum uric acid levels. Therefore, all serum uric acid samples were taken preoperatively before fluid preloading. Also estimation of blood loss by weighting gauzes or by hematocrit is extremely unreliable and was not done in our study.

CONCLUSION:

We conclude that elevated serum uric acid levels are associated with uterine atony as indicated by supplemental uterotonic agent use. Further studies are needed to confirm these findings and to determine whether this is associated with increased blood loss and whether normalisation of serum uric acid levels before elective surgery can help in reducing blood loss during caesarean delivery.

REFERENCES:

1. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet. 2001 Jan 6; 357(9249):53-6.
2. Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP. Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery. Am J Obstet Gynecol. 2006 Jan; 194(1):160.
3. Voto LS, Illia R, Darbon-Grosso HA, Imaz FU, Margulies M.Uric acid levels: a useful index of the severity of preeclampsia and perinatal prognosis. J Perinat Med. 1988; 16(2):123–6.
4. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, Powers RW,et al. Uric acid is as important as proteinuria in identifying foetal risk in women with gestational hypertension. Hypertension. 2005 Dec; 46(6):1263–9.
5. Masoura S, Makedou K, Theodoridis T, Kourtis A, Zepiridis L, Athanasiadis A. The involvement of uric acid in the pathogenesis of preeclampsia. Current Hypertension Reviews.2015;11(2):110-5.
6. Kang DH, Park SK, Lee IK, Johnson RJ.Uric acid induced C-reactive protein expression: implication on cell proliferation and nitric oxide production on human vascularcells. J Am Soc Nephrol. 2005; 16:3553-62.
7. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta. 2008 Mar; 29(Suppl A): S67-S72.
8. Simic M, Jovanovic S. Antioxidation mechanisms of uric acid. J Am Chem Soc. 1989 July 1; 111(15):5778–5782.
9. Hink HU, Santanam N, Dikalov S, Mccann L, Nguyen AD, Parthasarathy S et al. Peroxidase properties of extracellular superoxide dismutase: role of uric acid in modulating in vivo activity. Arterioscler Thromb Vasc Biol. 2002; 22:1402–8.
10. Abuja PM. Ascorbate prevents prooxidant effects of urate in oxidation of human low-density lipoprotein. FEBS Lett. 1999 Mar; 446(2-3):305–8.
11. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003 Jun 4; 41(6):1183–90.
12. Ekelund UE, Harrison RW, Shokek O, et al. Intravenous allopurinol decreases myocardial oxygen consumption and increases mechanical efficiency in dogs with pacing-induced heart failure. Circ Res 1999;85:437–45.
13. Saavedra WF, Paolocci N, St John ME, et al. Imbalance between xanthine oxidase and nitric oxide synthase signaling pathways underlies mechanoenergetic uncoupling in the failing heart. Circ Res 2002;90:297–304.
14. Cesselli D, Jakoniuk I, Barlucchi L, et al. Oxidative stress mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. Circ Res 2001;89:279–86.
15. Ukai T, Cheng CP, Tachibana H, et al. Allopurinol enhances the contractile response to dobutamine and exercise in dogs with pacing-induced heart failure. Circulation 2001;103:750–5.
16. Baldus S, Mullerleile K, Chumley P, et al. Inhibition of xanthine oxidase

improves myocardial contractility in patients with ischemic cardiomyopathy. Free Radic Biol Med 2006;41:1282–8.
17. Warren AY, Matharoo-Ball B, Shaw RW, Khan RN. Hydrogen peroxide and superoxide anion modulate pregnant human myometrial contractility. Reproduction 2005;130:539–44.
18. Goetzl L, Manevich Y, Roedner C, Praktish A, Hebbar L,Townsend DM. Maternal and fetal oxidative stress and intrapartum term fever. Am J Obstet Gynecol 2010;202.. 363 e1–5.
19. Young P, Johanson R. Haemodynamic, invasive and echocardiographic monitoring in the hypertensive parturient. Best Pract Res Clin Obstet Gynaecol 2001;15:605–22.
20. 36. Rouse DJ, Leindecker S, Landon M, et al. The MFMU caesarean registry: uterine atony after primary cesarean delivery. Am J Obstet Gynecol 2005;193:1056–60.
21. V.P. Kovacheva, M.A. Soens, L.C. Tsen. Serum uric acid as a novel marker for uterine atony and post-spinal vasopressor use during cesarean delivery. International Journal of Obstetric Anesthesia (2013) 22, 200–208
22. Bhatia N, Jain K, Sikka P, Verma I. Effect of maternal hyperuricemia on post-spinal hypotension and uterine tone in normotensive parturients undergoing non-elective cesarean delivery: a prospective observational study. Anesthesia & Analgesia. 2016 Sep;123(3S-suppl) :235.