Archives of Gynecology and Obstetrics (2019) 300:925–931
https://doi.org/10.1007/s00404-019-05282-x

MATERNAL-FETAL MEDICINE

Maternal hyperuricemia as a marker of post-spinal hypotension and uterine tone during cesarean delivery: a prospective observational study

Nidhi Bhatia[1] · R. Shanmugam[1] · Kajal Jain[1] · Pooja Sikka[2] · Indu Verma[3]

Received: 16 May 2018 / Accepted: 3 September 2019 / Published online: 14 September 2019

Abstract

Purpose Raised serum uric acid, a marker of oxidative stress, is known to increase vascular tone and depress myometrial contractility. A rise in serum uric acid levels has also been reported during labor, warranting its correlation with post-spinal hypotension and uterine tone.

Methods Serum UA sample was drawn from enrolled healthy, laboring parturients. Of these, 100 women who required emergency cesarean delivery were re-sampled prior to surgery. Following spinal anesthesia we recorded episodes of hypotension (MAP < 80% of baseline), use of vasopressors and supplemental uterotonics. The primary outcome was maternal hyperuricemia (1SD > appropriate for gestation age) and its correlation with post-spinal hypotension. Secondary outcomes were total vasopressors used, duration of labor and its effect on uric acid levels, uterine tone and neonatal outcome.

Results Hyperuricemia was observed in 33% of parturients. On comparing with women showing normal uric acid levels, hyperuricemic parturients experienced significantly lower incidence of post-spinal hypotension (45.5% vs. 67.2%; p value = 0.04) and lower vasopressor usage (p value = 0.06). Clinically, an increased use of supplemental uterotonics in these parturients was noted ($p = 0.20$). The duration of labor had no impact on uric acid levels. Neonatal outcome was unaffected.

Conclusions In healthy, normotensive parturients undergoing emergency cesarean delivery, maternal hyperuricemia is associated with lower incidence of post-spinal hypotension and reduced need of vasopressors. Elevated serum uric acid levels may also be associated with decreased uterine tone, necessitating greater requirement of supplemental uterotonics. However, further prospective trials are needed to strongly establish this association.

Keywords Emergency cesarean delivery · Maternal hyperuricemia · Post-spinal hypotension · Uterine tone

Introduction

Hypotension following subarachnoid block during cesarean section is undesirable as it is associated with adverse maternal (nausea, vomiting) and fetal (lower umbilical artery pH) implications [1]. Incidence of post-spinal hypotension increases from 33% in general population to almost 90% in pregnant women [2]. Parturients in established labor, who subsequently undergo spinal anesthesia for emergency cesarean section are known to have a lower incidence of post-spinal hypotension [3]. The exact reason for this association is, however, unknown. The stress of labor is known to result in an increased generation of reactive oxygen species (ROS) and increased serum uric acid (UA) levels through the process of repetitive ischemia and reperfusion during uterine contractile activity [4, 5]. A recent retrospective study [6] investigated the role of serum UA levels, a commonly requested laboratory investigation, in post-spinal hemodynamics of women undergoing neuraxial block for cesarean delivery. The authors reported a significant correlation between increased serum UA levels and lower vasopressor requirement. Increased serum UA levels were also

✉ Kajal Jain
kajalteji@gmail.com

[1] Department of Anesthesia and Intensive Care, Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[2] Department of Obstetrics and Gynecology, Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[3] Department of Biochemistry, Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

associated with depressed myometrial contractility, necessitating greater use of supplemental uterotonics following delivery. This prompted us to study the levels of serum UA in healthy, laboring women and evaluate its correlation with post-spinal hypotension and uterine tone. We hypothesized that parturients with serum UA levels one standard deviation greater than that appropriate for gestation age [7] may have a lower incidence of post-spinal hypotension and concurrent vasopressor usage. The primary outcome of our study was to evaluate the association between maternal hyperuricemia and the incidence of post-spinal hypotension. Our secondary outcomes included total dose of vasopressors used to maintain the targeted mean arterial blood pressure pre-delivery, duration of labor and its impact on serum UA levels, uterine tone post-delivery, use of supplemental uterotonics, intraoperative blood loss, neonatal birth weight and immediate neonatal outcome [by noting Apgar scores, analyzing cord blood for the presence of acidosis (pH < 7.2 or base excess − 12 meq/l) and recording the need for immediate neonatal resuscitation (bag-mask ventilation/short-term intubation)].

Methods

The study was approved by the Institute Ethics Committee (Intramural), [Chairperson: Prof. L.K. Dhaliwal; IEC No.: NK/1776/MD/10169-70], and written informed consent was obtained from all the subjects participating in the trial. The trial was registered at Clinical Trial Registry of India [registration number: CTRI/2015/04/005702 (URL: https://www.ctri.nic.in)]. It was a prospective, observational study. Healthy, laboring, primigravid women with term gestation, admitted to labor room for normal vaginal delivery were screened for inclusion. At this initial screening, their willingness to participate in the study was documented in a written informed consent form. Of these, parturients who underwent emergency cesarean delivery were included in the study. Women with hypertensive disorders of pregnancy, abnormal placentation, twin pregnancy, polyhydramnios, pre-existing medical disorders, coagulation abnormalities, prior known hyperuricemia, receiving epidural labor analgesia/general anesthesia were excluded from the study sample.

Data collection

The details of maternal history and baseline vital parameters were recorded. At this time, mean arterial pressure (MAP) measurements were taken for the purpose of obtaining a baseline value, with patients positioned supine with left lateral tilt. After a brief resting period, a mean of three consecutive values for which systolic blood pressure varied by < 10%, obtained 1 min apart, was taken as baseline MAP.

The intrapartum management and maternal monitoring was as per our institutional protocol. Intrapartum details such as nil oral status, labor augmentation with oxytocin, duration of labor, cervical dilatation at the time of initial screening, indication for cesarean delivery and relevant routine laboratory data (complete blood count, blood grouping) were also recorded. At initial screening, a 2 ml whole blood sample (S1) was drawn in a plain vial and sent for serum UA estimation (Beckman Coulter Analyser, Model-AU5811, Beckman Coulter India Private limited). Another similar sample was obtained prior to the conduct of cesarean delivery in the operating room (S2). Both S1 and S2 were drawn by an investigator blinded to intraoperative findings. Hyperuricemia was defined as a serum UA level one standard deviation greater than that appropriate for gestation age as defined by Lind et al. [7]. We chose serum UA levels corrected for gestational age because the UA levels during normal pregnancy are dynamic and fluctuate in a consistent pattern [8]. Pre-cesarean delivery serum UA values (S2) were used for analyzing our data.

Study protocol

At our institute, anesthesia for cesarean delivery is provided using a standard protocol. After starting intravenous (IV) lactated ringers solution infusion, all patients received anti-aspiration prophylaxis with IV metoclopramide 10 mg and ranitidine 50 mg prior to the start of surgery. Baseline standard monitoring was initiated in the operating room (S5/Avance, Datex Ohmeda, Inc Madison WI; 53707-7550 USA) and spinal anesthesia was administered with a 26G Quincke needle using 10 mg of 0.5% hyperbaric bupivacaine with 20 µg fentanyl. Following subarachnoid block, patients were placed supine with manual left uterine displacement. The level of block height achieved was determined by bilateral loss of sensation to cold. A level of T4–T6 was considered as adequate surgical anesthesia. Non-invasive blood pressure (NIBP) was recorded every minute till the birth of the baby and then at every 5 min interval. Intravenous 50 µg boluses of phenylephrine were administered to maintain maternal mean arterial pressure (MAP) > 80% of the baseline. Intravenous 3 mg boluses of mephentermine were given if hypotension was accompanied with bradycardia (HR < 50). Episodes of hypotension and total dose of vasopressors given up to the time of uterine incision were recorded. Vasopressor use was expressed in phenylephrine equivalents, which was the total amount of phenylephrine and mephentermine (converted at a ratio of mephentermine 1.2 mg = phenylephrine 100 µg) [9] used. Any incidence of nausea (reported spontaneously by patients) or vomiting (observed by investigators) was also recorded, and treated with injection ondansetron 4 mg IV, if needed, as per our hospital protocol.

On delivery of the baby, oxytocin infusion was started @ 0.3 IU/min (15 IU of oxytocin in 50 ml crystalloid solution @ 1 ml/min) using an infusion pump (INFUSOR 950-Emco Meditek private limited, Baroda, India) [8]. Following placental expulsion, uterine tone and contractility were assessed by an obstetrician at every 2 min interval for 10 min and were graded as satisfactory or unsatisfactory. Total dose of oxytocin infused to maintain a satisfactory uterine tone was recorded. Once the uterus contracted satisfactorily, oxytocin was infused @ 0.02–0.04 IU/min [8]. In cases of unsatisfactory uterine tone, use of additional uterotonics (intramuscular methylergometrine/carboprost or subcutaneous/per-rectal misprostol) as well as any other measures taken to manage uterine atony (such as uterine massage) were recorded.

Intraoperative blood loss was estimated using modified Gross formula [10], ABL = BV[Hct(i) − Hct(f)]/Hct(m), wherein ABL is the actual blood loss, BV is the total blood volume calculated from body weight (BV = body weight (in kg) × 70 ml/kg), hct(i), hct(f) and hct(m) are the initial, final and mean (of initial and final) hematocrit ,respectively.

Neonatal birth weight and outcome was assessed using Apgar scores, cord blood gases and need for immediate neonatal resuscitation. Postoperatively, in the recovery room, all vitals (blood pressure, pulse rate, oxygen saturation) were monitored and oxytocin infusion 3 IU/h (50 ml/h) was given as per our hospital protocol.

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 20.0 for Windows). Normality of data was checked by measures of Kolmogorov Smirnov tests of normality. Mean or median was calculated for all quantitative variables as appropriate and for measures of dispersion, standard deviation or IQR was calculated. Unpaired *t* test was applied to compare normally distributed continuous variables between two study groups. Mann–Whitney *U* test was applied to compare amount of total vasopressors used between the two groups. Comparison of mean UA levels in patients requiring no/moderate (phenylephrine equivalents upto 200 µg)/high vasopressors (phenylephrine equivalents > 200 µg) was done by using one way ANOVA followed by post hoc multiple comparisons using Bonferroni adjustment. For categorical variables, Chi-square test/Fisher's exact test was applied, as applicable. All statistical analysis tests were two tailed and p value < 0.05 was taken as significant with 95% confidence interval. Assuming a 60% incidence of post-spinal hypotension with ± 10% precision at 95% confidence levels, our sample size came out to be 93 patients. To account for possible drop-outs, we decided to include 100 patients in our study.

Results

This study was conducted in accordance with STROBE statement. The flow of participants in the study is depicted in Fig. 1. Of the women admitted to the labor room during the study period, $n = 469$ met the inclusion criteria and were subjected to a baseline sample S1. A second sample (S2) was drawn from those women who underwent emergency cesarean section ($n = 115/469$; Fig. 1). Baseline mean arterial pressure (MAP) at the time of obtaining S2, was 92.55 ± 10.95 mmHg. Demographic profile and labor characteristics of all patients were similar (Table 1). Of the recruited subjects, maternal hyperuricemia was observed in 33% of the parturients on admission to labor room (S1 = 5.92 ± 0.76 mg/dl) as well as prior to cesarean delivery (S2 = 6.07 ± 0.59 mg/dl); whereas 67% of the patients had normal UA levels (S1 = 3.53 ± 0.99; S2 = 3.53 ± 1.01 mg/dl) at both times of sampling. The mean cervical dilatation at the time of initial screening was 2.9 ± 0.4 cm. We did not find any significant correlation between change in UA levels and duration of labor (Fig. 2). The commonest indication for proceeding to cesarean delivery was non-reassuring fetal heart rate, with the next common indication being meconium stained liquor (Table 2).

We report an overall 60% incidence of post-spinal hypotension in our sample. On comparing with parturients showing normal UA levels, hyperuricemic parturients experienced significantly lower incidence of post-spinal hypotension (45.5% vs. 67.2%; p value = 0.04) as well as lower vasopressor usage (p value = 0.06) (Figs. 3, 4). Further, a significant percentage of hyperuricemic parturients (54.5% vs. 32.8%; $p = 0.04$) did not experience hypotension. Mean UA levels were significantly greater in patients not requiring any vasopressors as compared to those needing moderate to high vasopressors (Table 3). Following subarachnoid block, hyperuricemic patients had higher MAP over time as compared to the patients with normal serum uric acid levels (Fig. 5).

Supplemental uterotonics were administered to 31% of women, who were reported to have unsatisfactory uterine tone by the obstetrician. No statistically significant difference was noted between the percentage of hyperuricemic and non-hyperuricemic patients requiring uterotonics (39.4% vs 26.9%; $p = 0.20$). Of the 31 patients who required supplemental uterotonics, 20 patients received single uterotonic agent [12 from normal UA group (17.9%), 8 from hyperuricemic group (24.2%)] and 11 patients received more than one supplemental uterotonic agent [6 from normal UA group (9%), 5 from hyperuricemic group (15.2%)]. These differences did not show any statistical significance ($p = 0.42$).

There was no statistically significant difference in the mean actual blood loss between hyperuricemia parturients

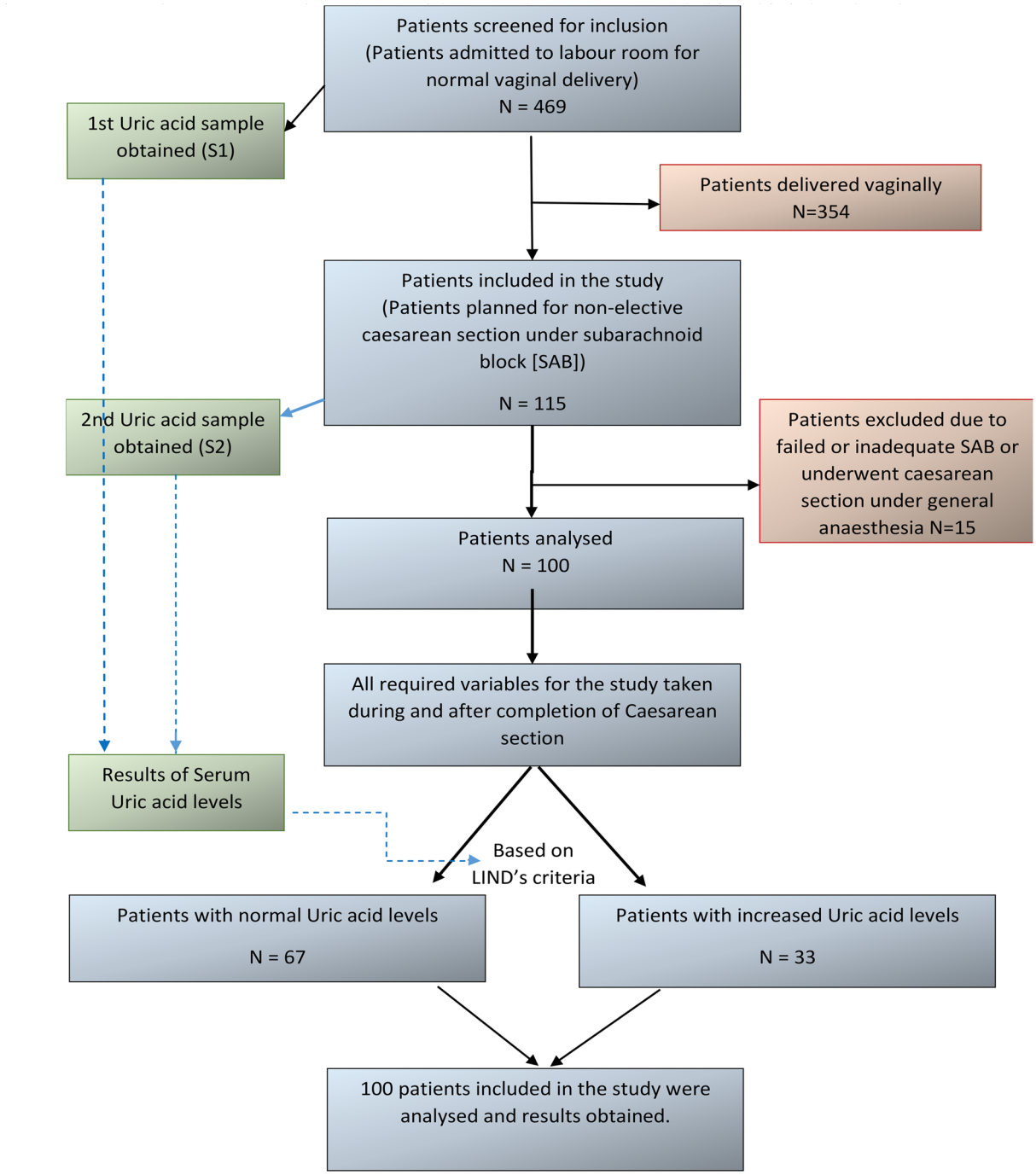


Fig. 1 Consort diagram

Our study showed that increased maternal serum UA values beyond physiological levels are associated with a decreased incidence of post-spinal hypotension during emergency cesarean delivery. It is well known that as compared to the general population, pregnant women have increased incidence of post-spinal hypotension. However, the incidence of hypotension in laboring parturients is decreased [3]. The ensure that other causes of altered uterine tone such as previous scar on uterus, twin gestation or coexisting diseases are excluded. A similar cohort of study sample and adherence to institutional protocol allowed us to rule out confounding factors such as starvation time, intravenous hydration and use of oxytocin which can influence maternal blood pressure.

Table 1 Demographic profile and labor characteristics

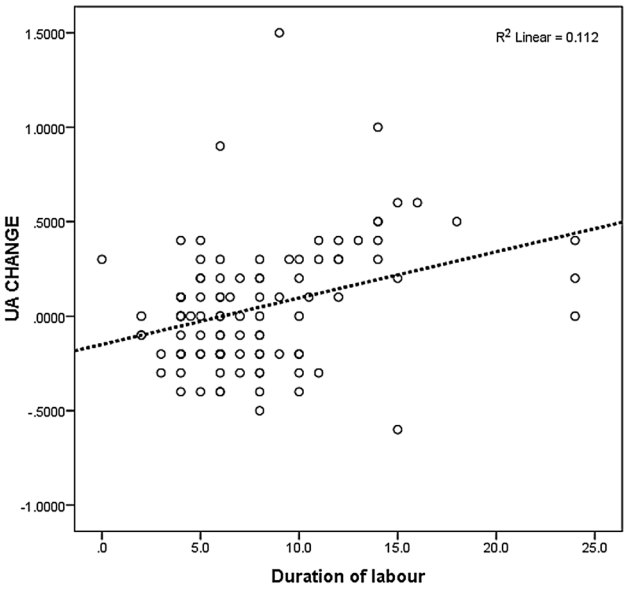
	All patients ($n=100$)	Patients with normal UA levels (pre-CD[b]) ($n=67$)	Patients with hyperuricemia (pre-CD[b]) ($n=33$)
Age (years)	26.28 ± 3.56	25.87 ± 3.54	27.12 ± 3.50
Gestational age (weeks)	37.06 ± 2.52	37.34 ± 2.34	36.48 ± 2.81
BMI[a] (kg/m^2)	26.1 ± 2.41	26.50 ± 2.47	25.55 ± 2.17
Hemoglobin (gm/dl)	11.26 ± 1.57	11.31 ± 1.59	11.15 ± 1.54
Duration of labor (h)	8.02 ± 4.54	7.88 ± 4.54	8.30 ± 4.59
Patients given oxytocin for labor induction (%)	36%	34.3%	39.3%

Values are expressed as mean ± SD and percentage

$p<0.05$ was taken as statistically significant

[a]Body mass index

[b]Cesarean delivery

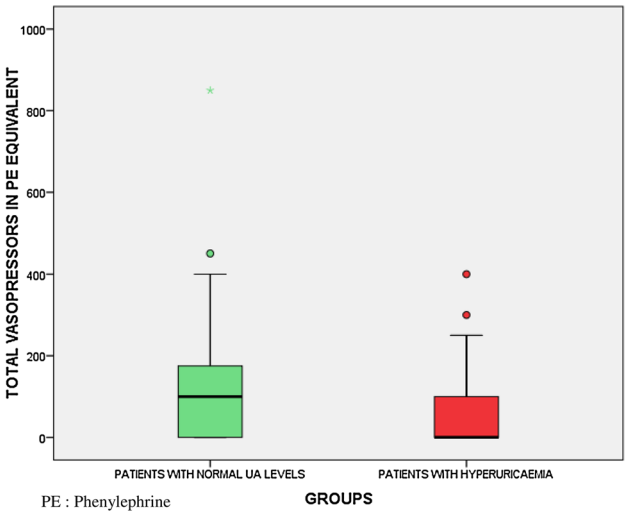


UA : Uric Acid

Fig. 2 Correlation between serum uric acid (UA) and duration of labor

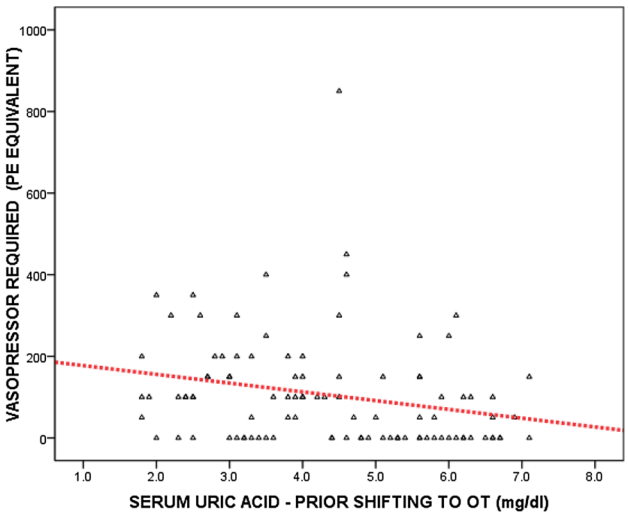
Table 2 Indications for emergency cesarean delivery

Indication for emergency cesarean delivery	Number of patients (%)
Non-reassuring fetal heart rate	43/100 (43%)
Meconium stained liquor	35/100 (35%)
Obstructed labor	7/100 (7%)
Non-progress of labor	6/100 (6%)
Unfavourable lie	6/100 (6%)
Cord prolapse	2/100 (2%)
Compound presentation	1/100 (1%)



PE : Phenylephrine

Fig. 3 Total vasopressors used in PE equivalent



PE : Phenylephrine

Fig. 4 Correlation between uric acid and vasopressor requirement

Table 3 Mean UA levels in patients requiring vasopressors

Vasopressors (VP) used	Number of patients	Mean pre-CD[a] UA levels (mg/dl) (mean ± SD)
No VP used	40	4.945 ± 1.39
Moderate VP used	46	3.996 ± 1.48
High VP used	14	3.950 ± 1.38

Using Bonferroni adjustment in multiple comparison, p value between no VP used and moderate VP used—0.003, between no VP used and high VP used—0.027, between moderate VP used and high VP used—0.917. Moderate vasopressors—phenylephrine equivalents upto 200 µg, high vasopressors—phenylephrine equivalents > 200 µg. $p < 0.05$ was taken as statistically significant

UA uric acid

[a]Cesarean delivery

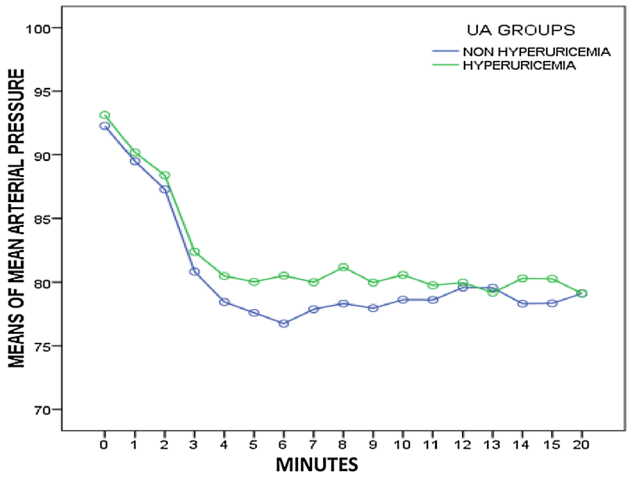


Fig. 5 Mean arterial pressure changes

The overall incidence of post-spinal hypotension was 60% in our study, which is less than what previous studies report (83%) [12]. We followed a standard anesthetic technique with current recommendations to manage maternal hypotension, which included a blood pressure reference range as well as use of phenylephrine The lower overall incidence of hypotension observed by us could have been due to the higher prevelance rate of hyperuricaemia in our study population (33% vs 25.4% in a study by Amini et al. [8]). We found a statistically significant decrease in the incidence of hypotension in patients with hyperuricaemia (45.5%) as opposed to those with normal serum UA levels (67.2%).

Asymptomatic hyperuricemia is commonly present in almost 20% of the general population, with it being a prevalent problem in pregnancy, inspite of presence of increased glomerular filtration rate [8]. The mechanism by which increased serum UA levels serve as a marker of hypertension maybe related to the synthesis of endothelial nitric oxide (NO) [13, 14]. UA is known to inhibit vasodilation in the lung by reducing endothelial cell NO production [14]. By impairing vasorelaxation, hyperuricaemia can decrease the requirement of vasopressors following subarachnoid block. This was also shown in a recent retrospective investigation by Kovacheva et al. [6] who reported a 33% prevelance rate of hyperuricemia, associated with increased vascular tone, in a heterogenous group of study population that included normotensive, hypertensive as well as preeclamptic parturients. The present data are a prospective observational study in a select common population of healthy, normotensive laboring women. We were unable to establish a strong association between the duration of labor and serum UA levels. Further, unlike previous retrospective analysis [6], we could not establish a strong association between serum UA levels and total amount of vasopressors required to maintain targeted mean arterial pressure following spinal anaesthesia. But, consistent with their findings, we also observed that elevated serum UA levels had a significant correlation to no vasopressor use, when compared with high vasopressor use.

Following delivery of the baby, uterotonics were required by 31% of our parturients for achieving a satisfactory uterine tone. As opposed to this, Kovacheva et al. [6] used supplemental uterotonics in only 10% of their patients. This difference could be due to varied institutional practices and subjective nature of uterine tone assessment, with the need of uterotonics at most of the times being decided by the operating obstetrician. Further, contrary to our findings, Kovacheva et al. [6] found a statistically significant correlation between high serum UA levels and increased need for supplemental uterotonics. This difference could be due to a larger number of patients ($n = 345$ vs $n = 100$ in our study) evaluated by Kovacheva et al., that included normotensive, hypertensive as well as preeclamptic parturients (as opposed to only normotensive parturients studied by us). Preeclamptic parturients are known to have high serum UA levels which might have caused an increased need for supplemental uterotonics.

All neonates in our study population had favorable Apgar scores and no significant neonatal cord blood pH changes. There are previous studies that have reported a rise in perinatal morbidity and mortality, along with higher incidence of intrauterine growth retardation, low birth weight and still birth with increased UA levels [15]. However, all of these studies have been conducted in pre-eclamptic parturients, which itself is a major risk factor for adverse neonatal outcome.

Our study had a few limitations. First, though supplemental uterotonics were administered to achieve the treatment goal of achieving satisfactory uterine tone, however the administration of uterotonics and measurement of uterine tone is highly subjective and depends on the treating

clinician. Second, serum UA levels may be influenced by time to last food intake. We measured UA levels at two time points: one on admission to labor suite and second prior to shifting for cesarean delivery. Though our patients were fasting prior to shifting for surgery, as per our labor and delivery protocols, however time to last food intake prior to admission to the labor room could not be controlled. Third, we are of the opinion that our sample size was inadequate to establish a strong correlation between serum uric acid levels and duration of labor experienced by the parturient. Finally, this study was not powered for detecting differences in neonatal outcome.

We conclude that in healthy, normotensive parturients undergoing emergency cesarean delivery, elevated serum uric acid levels are associated with lower incidence of post-spinal hypotension and reduced need of vasopressors. Elevated serum uric acid levels may also be associated with decreased uterine tone, necessitating greater requirement of supplemental uterotonics. However, further prospective trials are needed to strongly establish this association.

Author contributions NB: protocol development, data collection, data analysis, manuscript writing. RS: protocol development, patient recruitment, data collection and data analysis, manuscript writing. KJ: protocol development, data analysis and manuscript writing. PS: protocol development, data analysis, manuscript editing. IV: protocol development and data analysis, manuscript editing.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Bishop DG (2014) Predicting spinal hypotension during caesarean section. South Afr J Anaesth Analg 20(4):170–173
2. Montoya BH, Oliveros CI, Moreno DA (2009) Managing hypotension induced by spinal anesthesia for caesarean section. Rev Col Anest Mayo Julio 37(2):131–140
3. Lapins E (2001) Hypotension during spinal anaesthesia for caesarean section. Int J Obstet Anesth 10:226
4. Sharma RK, Agarwal A (2004) Role of reactive oxygen species in gynecologic diseases. Reprod Med Biol 3:177–199
5. Lam C, Lim KH, Kang DH, Karumanchi SA (2005) Uric acid and preeclampsia. Semin Nephrol 25:56–60
6. Kovacheva VP, Soens MA, Tsen LC (2013) Serum uric acid as a novel marker for uterine atony and post-spinal vasopressor use during cesarean delivery. Int J Obstet Anesth 22:200–208
7. Lind T, Godfrey KA, Otun H, Philips PR (1984) Changes in serum uric acid concentrations during normal pregnancy. Br J Obstet Gynaecol 91:128–132
8. Amini E, Sheikh M, Hantoushzadeh S, Shariat M, Abdollahi A, Kashanian M (2014) Maternal hyperuricemia in normotensive singleton pregnancy, a prenatal finding with continuous perinatal and postnatal effects, a prospective cohort study. BMC Pregnancy Childbirth 18:104
9. Mohta M, Janani SS, Sethi AK, Agarwal D, Tyagi A (2010) Comparison of phenylephrine hydrochloride and mephenteramine sulphate for prevention of post-spinal hypotension. Anaesthesia 65:1200–1205
10. Spahn DR (2000) Perioperative transfusion triggers for red blood cells. Vox Sang 78(2):163–166
11. Crawford MD (1939) The effect of labour on plasma uric acid and urea. BJOG 46:540–553
12. Rout CC, Rocke DA (1994) Prevention of hypotension following spinal anesthesia for cesarean section. Int Anesthesiol Clin 32:117–135
13. Bainbridge SA, Roberts JM, Versen-Höynck FV, Koch J, Edmunds L, Hubel CA (2009) Uric acid attenuates trophoblast invasion and integration into endothelial cell monolayers. Am J Physiol Cell Physiol 297:C440–C450
14. Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER et al (2008) Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. Am J Physiol Cell Physiol 295:C1183–C1190
15. Mustaphi R, Gopalan S, Dhaliwal L, Sarkar AK (1996) Hyperuricemia and pregnancy induced hypertension-reappraisal. Indian J Med Sci 50:68–71