Hypertension: *Original Research*

Nonsteroidal Antiinflammatory Drug Administration and Postpartum Blood Pressure in Women With Hypertensive Disorders of Pregnancy

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OBJECTIVE: To evaluate whether postpartum nonsteroidal antiinflammatory drug (NSAID) administration is associated with increased blood pressure in women with hypertensive disorders of pregnancy and to estimate the association between NSAID administration and use of opioid medication.

METHODS: We conducted a retrospective cohort study of women with hypertensive disorders of pregnancy. Patients were analyzed in two groups according to whether they received NSAIDs postpartum. Study participants were women delivered at a tertiary care center from 2008 to 2015. The primary outcome was change in mean arterial pressure during the postpartum period. Secondary outcomes were postpartum pain scores, cumulative postpartum opioid requirement, initiation or dose escalation of antihypertensive agents, and adverse postpartum outcomes including acute renal failure, change in hematocrit, and maternal readmission for hypertensive disorder.

RESULTS: Two hundred seventy-six women with hypertensive disorders of pregnancy were included (129 NSAID-unexposed and 147 NSAID-exposed). Postpartum NSAID administration was not associated with a statistically significant change in mean arterial pressure compared with no NSAID administration (−0.7 vs −1.8; mean difference 1.10, 95% CI −1.44 to 3.64). Similarly, no difference was observed between the cohorts in terms of need for initiation or escalation in dose of antihypertensive agents or maternal readmission for hypertensive disorder. The study was underpowered to determine whether NSAID administration was associated with any difference in less frequent secondary outcomes (eg, incidence of acute renal insufficiency, need for postpartum transfusion) or cumulative opioid use.

CONCLUSION: Nonsteroidal antiinflammatory drug administration to postpartum patients with hypertensive disorders of pregnancy is not associated with a change in blood pressure or requirement for antihypertensive medication.

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Hypertensive disorders of pregnancy (gestational hypertension; preeclampsia; eclampsia; hemolysis, elevated liver enzymes, low platelet count syndrome; chronic hypertension; and superimposed preeclampsia) complicate 10% of pregnancies.[1] In 2013, the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy issued a recommendation against use of nonsteroidal antiinflammatory drugs (NSAIDs) in women with

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hypertensive disorders of pregnancy that persist greater than 24 hours after delivery, suggesting these agents contribute to increased blood pressure (BP).[2] In nonobstetric populations, NSAIDs are well known to contribute to a small but significant increase in BP, which seems to be more pronounced in those on antihypertensive therapy. The mechanism of action is likely through NSAID inhibition of renal prostaglandins, leading to increased intravascular volume.[3,4]

Ascertaining the safety of NSAIDs during the postpartum period for women with hypertensive disorders of pregnancy is of clinical importance, because NSAIDs are a mainstay of analgesia for postpartum and postcesarean patients. Avoidance of NSAIDs typically results in use of alternative medication such as acetaminophen, opioid pain medications, or other pain adjuncts (eg, gabapentin, lidocaine patch). Increasing the use of opioid pain medication is particularly problematic in light of the present opioid use disorder epidemic. Evaluating the safety of NSAID administration for postpartum women with hypertensive disorders is therefore important.

We aimed to evaluate whether the administration of NSAIDs postpartum to women with hypertensive disorders of pregnancy was associated with worsening of hypertension postpartum. Secondarily, we also aimed to evaluate the association between receipt of postpartum NSAIDs and consumption of opioid pain medication.

MATERIALS AND METHODS

This was a retrospective cohort study of women with hypertensive disorders of pregnancy delivered at Thomas Jefferson University Hospital between January 2008 and May 2015. This study was approved by the institutional review board at Thomas Jefferson University. Patients with hypertensive disorders of pregnancy were identified from the electronic medical record using International Classification of Diseases, 9th Revision codes (Box 1). Patient charts were reviewed to determine the patient's hypertensive disorder according to the 2013 Hypertension Task Force definitions.

Box 1. International Classification of Diseases, 9th Revision Codes for Hypertensive Disorders of Pregnancy

Chronic hypertension (642.0, 642.1, 642.2, 642.9)
Gestational hypertension (642.3)
Preeclampsia (642.4)
Severe preeclampsia (642.5)
Superimposed preeclampsia (642.7)
Eclampsia (642.6)

Maternal demographic information as well as clinical data were abstracted by two authors (S.M. and A.B.). Training on data abstraction was provided by maternal–fetal medicine physicians (H.B.A. and A. R.), and data abstraction was initially overseen until accurate independent abstraction was achieved. Data abstraction questions or inconsistencies were resolved by a physician on review of the medical record. Data were stored in a secure REDCap database. Demographic data collected included maternal age, race, parity, and gestational age at delivery. Maternal medical characteristics (mode of delivery, medical comorbidities such as hypertension, diabetes, autoimmune disease, preexisting renal disease, tobacco use) were recorded. Preexisting renal disease was defined if either a previous renal diagnosis had been established by a nephrologist or the patient had proteinuria (greater than 300 mg per 24-hour urine protein or urine protein:creatinine ratio greater than 0.3) or elevation in creatinine 1.0 mg/dL or greater before 20 weeks of gestation. The patient's hypertensive diagnosis, according to the American College of Obstetricians and Gynecologists' 2013 definitions, was recorded as well as whether maternal magnesium sulfate was administered for seizure prevention.

Data from the inpatient postpartum course were also abstracted from the electronic medical record, including all systolic and diastolic BP values, all patient-reported pain scores (on a 10-point Likert scale), receipt of any NSAID pain medication (including medication received and number of doses), cumulative dose of postpartum opioid pain medication received (in morphine milligram equivalents), and receipt of antihypertensive agents postpartum. Patient-controlled administration doses of intravenous opioid medications were excluded from this calculation, because these data were recorded in a separate anesthesia electronic medical record that was not accessible to the investigators. Other variables with a potential effect on postpartum pain control (including delivery anesthesia, receipt of methadone maintenance therapy, and use of any adjunctive pain medications) were recorded as well. All postpartum patients delivered at our institution receive the same medication orders set for postpartum analgesia. Epidural catheters are removed in the delivery room after vaginal delivery and in the operating room after cesarean delivery. Intrathecal morphine is not used at our institution. Postcesarean patients are initially managed with an intravenous opioid patient-controlled analgesia on the day of delivery and on postoperative day 1 are transitioned to oral medications. Oral analgesics ordered postpartum and postoperatively include ibuprofen as well as oxycodone–acetaminophen

(Percocet), both administered as needed. The patient and her nurse use shared decision-making to determine individual dosing and frequency. In general, this process involves an NSAID taken for mild to moderate pain and addition of opioid medication at the lowest effective dose for the shortest amount of time for severe pain. Data on adverse postpartum outcomes potentially associated with worsening hypertension as well as with NSAID administration were also abstracted from the electronic medical record, including incidence of postpartum acute renal insufficiency (defined as rising postpartum creatinine or new renal diagnosis established by a nephrologist postpartum), need for postpartum transfusion, and readmission within 30 days for a hypertensive disorder.

Patients were analyzed in two cohorts according to whether or not they received postpartum NSAIDs. Fifteen hundred patient charts met study inclusion criteria. The majority of patients identified received postpartum NSAIDs. One hundred forty-seven NSAID-unexposed patients and 1,353 NSAID-exposed patients were identified. A subset of NSAID-exposed patients was identified by matching these patients one to one to NSAID-unexposed patients chronologically on the basis of the date of admission. Patients with missing or incomplete BP data were then excluded, resulting in a final study population of 129 NSAID-unexposed and 147 NSAID-exposed patients for analysis.

The primary outcome was the change in mean arterial pressure (MAP) in mm Hg, defined as the mean MAP from postpartum day 1 until the day of discharge minus the mean MAP on the day of delivery (postpartum day zero). Mean arterial pressure was chosen as a primary outcome because it is affected by both systolic and diastolic BP, which are equally clinically significant for obstetric patients with hypertensive disorders. Using data from Wasden et al, we performed an a priori power calculation and determined that 126 patients would be needed in each group to detect a difference between the groups in ΔMAP as small as 3 mm Hg (assuming $\alpha=0.05$, $\beta=0.15$, and SD 7.9 mm Hg).[2] A Mann-Whitney test was performed for continuous variables, and Fisher exact test was performed for categorical variables using Graphpad software.

Post hoc subgroup analyses by mode of delivery and in women with and without chronic hypertension were performed.

RESULTS

Two hundred seventy-six women with a hypertensive disorder of pregnancy comprised our study population (Table 1). The study cohorts were similar with respect to their demographic and medical characteristics, except that patients who did not receive NSAIDs were more likely to have preexisting renal disease (12% vs 2%, $P<.01$) than those who received NSAIDs. Women who received NSAIDs were more likely to be on antihypertensive medication antepartum (most commonly labetalol) than those not receiving NSAIDs (35% vs 22%, $P=.01$).

There was no statistically significant difference in the primary outcome, ΔMAP, between patients who did and did not receive NSAIDs (−0.7 vs −1.8; mean difference 1.10, 95% CI −1.44 to 3.64; Table 2). Both cohorts experienced a decline in BP between the day of delivery and the remainder of their inpatient postpartum course as evidenced by the negative values of ΔMAP for both cohorts. Similarly, there were no differences in change in systolic or diastolic pressure or maximum systolic or diastolic BP between the groups (Table 2).

There was no difference in rate of initiation or dose escalation of antihypertensive agents or other adverse postpartum events between the cohorts. Adverse postpartum outcomes including acute renal insufficiency, need for blood transfusion, and hospital readmission for a hypertensive disorder did not differ between the groups. This study was not adequately powered to detect changes in these secondary outcomes, however.

Similar pain scores were reported between both study groups postpartum (Table 3). Cumulative opioid use postpartum for women not receiving NSAIDs compared with those receiving NSAIDs was 465 compared with 341 morphine milliequivalents, respectively, which is not statistically different (mean difference 124.00, 95% CI −559.90 to 807.90). Forty-five percent of patients received additional adjunctive pain medications postpartum in addition to ibuprofen, oxycodone, or hydromorphone that are standard orders. The most common additional analgesic received was acetaminophen. There was no difference between groups in receipt of additional analgesic options overall or by individual agent received (Table 3). Other factors that could affect the need for postpartum analgesic agents, including delivery analgesia and use of methadone maintenance therapy, did not differ between cohorts. No difference in any of the BP or opioid use outcomes was noted when patients were stratified by route of delivery or presence or chronic hypertension (Appendices 1 and 2, available online at http://links.lww.com/AOG/B191).

Table 1. Maternal Demographics

	No NSAIDs (n=129)	NSAIDs (n=147)	*P*
Maternal age (y)	29.4±6.0	30.1±6.7	.38
Gestational age at delivery (wk)	35.9±4.4	37.1±3.0	.07
Cesarean delivery	43 (33)	62 (42)	.06
Multiparity	53 (41)	51 (35)	.31
BMI 30 kg/m^2 or greater	50/110 (46)	69/124 (56)	.15
Ethnicity			
White	27 (21)	23 (16)	.20
African American	85 (66)	102 (69)	.60
Asian	10 (8)	8 (5)	.40
Hispanic	1 (1)	2 (1)	1.0
Other	6 (5)	12 (8)	.30
Preexisting renal disease	16 (12)	3 (2)	**<.01**
Pregestational diabetes	14 (11)	9 (6)	.19
Gestational diabetes	15 (12)	16 (11)	.85
Autoimmune disease	5 (4)	2 (1)	.25
Smoking	17 (13)	20 (14)	1.0
Hypertensive diagnosis			
Chronic HTN	64 (50)	60 (41)	.11
On antihypertensive medication at admission	28 (22)	52 (35)	**.01**
Gestational HTN	28 (22)	29 (20)	.76
Preeclampsia	15 (12)	29 (20)	.07
Preeclampsia with severe features	22 (17)	27 (19)	.80
Chronic HTN with superimposed preeclampsia	4 (3)	5 (3)	1.0
Chronic HTN with superimposed preeclampsia with severe features	28 (17)	19 (13)	.056
Eclampsia	0 (0)	1 (0.5)	1.0
Received magnesium sulfate	46 (36)	43 (30)	.3

NSAIDs, nonsteroidal antiinflammatory drugs; BMI, body mass index; HTN, hypertension.
Data are mean±SD, n (%), or n/N (%) unless otherwise specified.
Bold indicates statistically significance.

DISCUSSION

Our data suggest that administration of NSAIDs postpartum to women with hypertensive disorders of pregnancy is not associated with worsening hypertension and may be associated with less consumption of opioid pain medications during the inpatient postpartum course. These findings are in agreement with a growing body of obstetric literature suggesting that postpartum NSAID administration is not associated with adverse effects on BP for women with hypertensive disorders of pregnancy. In nonpregnant individuals, the adverse effect of long-term use of NSAIDs on hypertension is well known.[5] This effect is particularly pronounced in patients on antihypertensive therapy.

Table 2. Postpartum Outcome Data

	No NSAIDs (n=129)	NSAIDs (n=147)	*P*
ΔMAP (mm Hg)	−0.7±10.7	−1.8 ±10.8	.31
MAP postpartum day 1 (mm Hg)	94.1 ±10.6	93.2±21.5	.68
MAP postpartum day 2 to discharge	93.6±16.4	92.2 ±16.8	.53
ΔSystolic BP (mm Hg)	−0.2±28.4	1.4±33.7	.62
ΔDiastolic BP (mm Hg)	−0.4±17.8	1.4±19.1	.43
Maximum postpartum systolic BP (mm Hg)	148.6±23.4	147.1±24.4	.65
Maximum postpartum diastolic BP (mm Hg)	92.4±16.4	90.6±16.2	.34
Postpartum initiation or dose increase of antihypertensive agent	42 (33)	44 (30)	.69
Postpartum readmission for hypertensive disorder	2 (2)	1 (0.6)	.66
Acute renal insufficiency	7 (5)	4 (3)	.35
Postpartum transfusion	5 (4)	4 (3)	.73

NSAIDs, nonsteroidal antiinflammatory drugs; MAP, mean arterial pressure; BP, blood pressure.
Data are mean±SD or n (%) unless otherwise specified.

Table 3. Postpartum Pain Scores and Analgesic Medications Administered

	No NSAIDs (n=129)	NSAIDs (n=147)	*P*
Cumulative opioid dose (morphine milliequivalents)	465±3,797	341±1,212	.72
Mean pain score (1–10) points reported	2.2±1.7	2.5±1.6	.07
Methadone maintenance	2 (2)	6 (4)	.32
Delivery anesthesia			
Regional	99 (77)	125 (85)	.09
General	6 (5)	2 (1)	.15
Adjunctive pain medications received*	55 (43)	69 (47)	.54
Gabapentin	2 (1.5)	1 (0.5)	.60
Nalbuphine	6 (4.5)	15 (10)	.10
Fioricet	10 (8)	9 (5)	.60
Acetaminophen	28 (22)	34 (23)	.90
Tramadol	6 (4.5)	1 (0.5)	.05
Meperedine	2 (1.5)	3 (4.5)	1.0
Lidocaine	0 (0)	1 (1.5)	1.0

NSAIDs, nonsteroidal antiinflammatory drugs.
Data are mean±SD or n (%) unless otherwise specified.
* All opioid medications were factored into total morphine milliequivalents calculation.

However, short-term use of NSAIDs is not associated with the same effect on BP. Furthermore, the individual NSAIDs seem to differentially affect BP with naproxen and indomethacin being associated with the largest increases in BP.[4]

In 2004, a case series published by Makris et al suggested NSAIDs may be dangerous in pregnant women with hypertensive disorders. Six patients were presented who developed hypertensive urgency after receipt of NSAIDs (four of six received indomethacin).[6] However, contemporary studies with control groups have not found an association between NSAIDs and hypertensive urgency. A retrospective cohort study (223 women) by Wasden et al[7] found no difference in postpartum MAP or adverse postpartum events in women with severe preeclampsia who received NSAIDs compared with controls who did not. Another retrospective cohort study by Viteri et al (324 women) yielded similar findings: no significant difference in severe hypertension or adverse postpartum outcomes among women with severe preeclampsia who received NSAIDs compared with those who did not. No difference was observed between cohorts in use of opioid pain medication.[8] Vigil-De Gracia et al conducted a randomized controlled trial among women with superimposed preeclampsia or preeclampsia with severe features. Patients were randomized to receive ibuprofen or acetaminophen for postpartum analgesia. Although more postpartum hypertension was noted among women randomized to ibuprofen, there was no difference in severe hypertension between the groups.[9] Most recently, Blue et al reported no difference both immediately postpartum and at 6 weeks postpartum in multiple BP parameters in women with severe preeclampsia randomized to ibuprofen compared with acetaminophen. They found no difference in opioid use between the groups.[10]

Our study has a number of limitations, including its retrospective study design and a sample size inadequate to detect differences in infrequent postpartum adverse outcomes. Our study was also limited by the short-term follow-up of study participants (until hospital discharge).

Strengths of the study include being adequately powered for our primary outcome to detect a difference as small as 3 mm Hg between the groups, which would represent a clinically significant difference in BP (to change MAP by 3 mm Hg, systolic BP would need to change by 9 mm Hg or diastolic BP by 4 mm Hg). The inclusion of an ethnically diverse population as well as a broad spectrum of all hypertensive disorders of pregnancy make our study results reasonably generalizable.

In summary, NSAID administration to postpartum patients with hypertensive disorders of pregnancy is not associated with an increase in BP or increased requirement for antihypertensive medication. These findings lead us to question the recommendation against use of NSAIDs postpartum in women with hypertensive disorders of pregnancy. Larger studies, or meta-analysis of existing studies, may shed further light on rare adverse outcomes, which individual studies to date have been underpowered to evaluate.

REFERENCES

1. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens Res 2017;40:213–20.
2. Executive summary: hypertension in pregnancy. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1122–31.
3. White WB. Cardiovascular effects of the cyclooxygenase inhibitors. Hypertension 2007;49:408–18.
4. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993;153:477–84.
5. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289–300.
6. Makris A, Thornton C, Hennessy A. Postpartum hypertension and nonsteroidal analgesia. Am J Obstet Gynecol 2004;190:577–8.
7. Wasden SW, Ragsdale ES, Chasen ST, Skupski DW. Impact of non-steroidal anti-inflammatory drugs on hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4:259–63.
8. Viteri OA, England JA, Alrais MA, Lash KA, Villegas MI, Ashimi Balogun OA, et al. Association of nonsteroidal antiiflamatory drugs and postpartum hypertension in women with preecclampsia with severe features. Obstet Gynecol 2017;130: 830–5.
9. Vigil-De Gracia P, Solis V, Ortega N. Ibuprofen versus acetaminophen as a post-partum analgesic for women with severe pre-eclampsia: randomized clinical study. J Matern Fetal Neonatal Med 2017;30:1279–82.
10. Blue NR, Murray-Krezan C, Drake-Lavelle S, Weinberg D, Holbrook BD, Katuri VR, et al. Effect of ibuprofen vs acetaminophen in postpartum hypertension in preeclampsia with severe features: a double-masked, randomized controlled trial. Am J Obstet Gynecol 2018;218:616.e1–8.