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Original Article

Impact of non-steroidal anti-inflammatory drugs on hypertensive disorders of pregnancy

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ABSTRACT

Objective: Non-steroidal anti-inflammatory drug (NSAID) use has the potential to adversely affect blood pressure in women with hypertensive disorders of pregnancy. We sought to evaluate this association.

Study design: Women affected with severe hypertensive disorders of pregnancy were identified by retrospective chart review. The medication administration record was then used to identify controls (no NSAID exposure) until a sufficient number of patients were obtained, after which the cases (NSAID exposed) were identified in a chronological manner during the same study period until a 2:1 ratio was achieved. The primary outcome was the change in mean of all postpartum mean arterial pressures (MAP) throughout the hospital stay. Power analysis showed that 146 exposed and 73 unexposed subjects were necessary to obtain 90% power to detect a MAP difference of 10 mmHg between the groups. Secondary outcomes included: initiation of anti-hypertensive medication, need for increased doses of anti-hypertension medication, and adverse events related to hypertension.

Results: 223 women had severe hypertensive disorders of pregnancy, of whom 75 (34%) were not exposed to NSAIDs and 148 (66%) were exposed. NSAID exposure was not associated with a difference in the average MAP postpartum ($p = 0.70$), nor any of the secondary outcomes evaluated. Exposure to NSAIDs was less likely as serum creatinine increased ($p = 0.012$).

Conclusion: In women with severe hypertensive disorders of pregnancy, NSAIDs did not appear to increase the average postpartum MAP, increase the requirement for anti-hypertensive medications, or increase the rate of adverse postpartum events.

Introduction

Hypertensive disorders of pregnancy, including preeclampsia, gestational hypertension, chronic hypertension and chronic hypertension with superimposed preeclampsia, complicate approximately 10 percent of pregnancies [1]. While most hypertensive disorders of pregnancy can be safely managed with low risk of complications, affected patients, especially those with severe preeclampsia, severe gestational hypertension and chronic hypertension with superimposed preeclampsia (severe

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hypertensive disorders of pregnancy), are at higher-risk for adverse maternal and perinatal complications [2].

The definitive treatment for preeclampsia or gestational hypertension is delivery. After delivery, pain control is an essential component of patient care for both vaginal and cesarean deliveries [3–5]. Typically pain relief is provided by regional anesthesia (i.e. patient controlled epidural anesthesia), systemic narcotic administration, acetaminophen, and/or non-steroidal anti-inflammatory drugs (NSAID) [3]. Purported benefits of NSAID use include minimizing narcotic associated side-effects, improved pain relief from uterine cramping or involution, and complementing other analgesic medications or methods [3,5]. However, NSAID use is associated with increases in blood pressure in both hypertensive and non-hypertensive patients [6]. While this relationship is well established and accepted in older patients with other co-morbidities [7], NSAID use has also been associated with hypertension in young women [8]. Possible mechanisms include NSAID inhibition of prostaglandins acting as vasodilators [9], decreased renal sodium excretion (natriuresis) secondary to prostaglandin E2 inhibition [10,11], and NSAIDs leading to arachidonic acid metabolism by cytochrome P450 with production of metabolites containing vasoconstrictive properties [6,12].

Given the biologic plausibility and the association of NSAID use and hypertension, the recent executive summary of hypertension in pregnancy published by the American Congress of Obstetricians and Gynecologists suggested discontinuation of NSAIDs in patients with hypertension that persists for more than 1 day postpartum [13]. However, the effect of NSAID use on blood pressure in this particular population remains poorly studied and speculative [14,15]. Given the above associations and recommendations, we sought to evaluate if NSAID use in patients with hypertensive disorders of pregnancy was associated with blood pressure changes postpartum. Because the blood pressure effects appear most pronounced in those with existing hypertension and underlying renal disease [16,17], we hypothesized that patients with severe hypertensive disorders of pregnancy exposed to NSAIDs would have significantly elevated blood pressure postpartum compared to similar patients not exposed to NSAIDs.

Materials and methods

This is a retrospective cohort study evaluating women with severe hypertensive disorders of pregnancy, and was approved by the institutional review board at Weill Cornell Medical College. At our institution women with severe hypertensive disorders of pregnancy are typically treated with magnesium sulfate for seizure prophylaxis, while patients with mild hypertensive disorders of pregnancy typically do not receive magnesium sulfate. Patients with severe hypertensive disorders of pregnancy were identified through pharmacy records using magnesium sulfate administration as a surrogate marker for severe disease. We analyzed the medication administration record in patient care areas where magnesium sulfate is used for seizure prophylaxis from 2008 to 2009, and confirmed that magnesium sulfate was administered for seizure prophylaxis by record review. Patients that received magnesium sulfate for other indications were excluded. Patient charts were reviewed and NSAID use was determined and cases (NSAID exposed) and controls (no NSAID exposure) were included. Controls were identified through the medication administration record until a sufficient number were obtained, after which NSAID exposed patients were identified in a chronological manner during the same study period until a 1:2 ratio was achieved.

Demographic information was extracted from the chart as well as parity, gestational age at delivery, tobacco use during the pregnancy, pre-gestational or gestational diabetes, medical conditions complicating pregnancy, mode of delivery, days of hospitalization after delivery, and the serum creatinine prior to delivery. Use and dose of all anti-hypertensive medications and NSAIDs were recorded. The first postpartum mean arterial pressure (MAP) measurement, baseline MAP, and then each subsequent MAP measurement in the postpartum period during the hospitalization were recorded. Instruments were calibrated as per the protocol of our biomedical department. MAP was taken by clinical staff (registered nurses). The MAP was obtained with the patient in a semi-Fowler or seated position, with the blood pressure cuff at the level of the patient's heart. During the study period Welch Allyn, Tycos mobile sphygmomanometers were used. The blood pressure cuff was adjusted depending on the size of the patient's arm. In our institution manual blood pressure measurements are obtained on patients with hypertensive disorders of pregnancy – automated machines are not typically used.

The primary outcome evaluated was the difference in the mean of all postpartum MAP in the NSAID unexposed and exposed groups. Secondary outcomes included: Initiation of anti-hypertensive medication postpartum, need for increased doses of anti-hypertensive medications postpartum, length of hospital stay after delivery, and adverse events related to hypertension. Adverse events related to hypertension included cerebral vascular accident, admission to the intensive care unit for blood pressure control, pulmonary edema, eclampsia and readmission to the hospital for hypertension.

To evaluate the primary outcome we used a ratio of 2:1 for patients exposed to NSAIDs and those not exposed to NSAIDs, respectively. We calculated that we would need 146 exposed patients and 73 unexposed to obtain 90% power to detect a MAP difference of 10 mmHg between the groups. Prior studies have shown a MAP change up to 4–6 mmHg with NSAID use [16–18]. We estimated that a change of 5 mmHg would not be clinically significant for this generally young and healthy population with blood pressure measured over a period of days (instead of months to years for the elderly where this level might lead to morbidity or increased use of medications). Chi-SQUARE test and Student's *T* test were used for comparison. Spearman's rho was used to evaluate correlations, and Mann–Whitney *U* test was used to compare the total dose of NSAID used and need for anti-hypertensive medication