Title
Timely Treatment of Severe Maternal Hypertension and Reduction in Severe Maternal Morbidity

Author
Gupta, Megha

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Timely Treatment of Severe Maternal Hypertension and Reduction in Severe Maternal Morbidity

A dissertation submitted in partial satisfaction of the requirements for the degree Master of Science in Clinical Research

by

Megha Gupta

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ABSTRACT OF THE DISSERTATION

Timely Treatment of

Severe Maternal Hypertension and

Reduction in Severe Maternal Morbidity

by

Megha Gupta

Master of Science in Clinical Research

University of California, Los Angeles, 2018

Professor Marc Adam Suchard, Chair

Objective: To determine if timely treatment within 60 minutes of confirmed diagnosis of severe maternal hypertension with antihypertensive medications was associated with reduction in severe maternal morbidity.

Methods: Medical records of women with severe hypertension (at least two severe blood pressures, systolic ≥160mmHg and/or diastolic ≥110mmHg, within 60 minutes) were accessed for timing of severe blood pressures, timing of treatment, and blood pressure response to treatment. Severe maternal morbidity was confirmed by multidisciplinary case review. We compared the incidence of severe maternal morbidity between women who received timely (within 60 minutes of diagnosis) vs. not-timely treatment.

Results: Of 465 women with severe hypertension, 29 (6.2%) experienced severe maternal morbidity. Fifty-six percent of women received timely treatment, of whom 1.9% had severe maternal morbidity, compared with 6.4% of women who did not receive timely treatment (p=0.02). Timely treatment was associated with a 72% reduction in relative odds of severe maternal morbidity (p=0.02). No significant difference was seen in median pre-treatment systolic pressures (p=0.20) between the groups.

Conclusion: Antihypertensive treatment within 60 minutes of confirmed diagnosis of severe hypertension was associated with reduction in severe maternal morbidity. Our findings support current recommendations to treat all women with severe hypertension with antihypertensive medications in a timely fashion.

The thesis of Megha Gupta is approved.

David Elashoff

Kimberly D. Gregory

Sarah J. Kilpatrick

Marc A. Suchard, Committee Chair

University of California, Los Angeles

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INTRODUCTION

Hypertensive disorders of pregnancy are leading causes of maternal morbidity and mortality, responsible for up to 10% of cases of severe maternal morbidity (SMM) and 16% of maternal deaths in the United States[1-3] Current guidelines from American College of Obstetricians and Gynecologists (ACOG) and California Maternal Quality Care Collaborative (CMQCC) recommend initiating treatment of acute-onset sustained severe hypertension with antihypertensive medications within 60 minutes of the second severe blood pressure.[4-6] These recommendations, however, are based only on a case series of 28 women who suffered a stroke associated with severe preeclampsia or eclampsia, whose mean systolic blood pressure (SBP) was 175 mmHg and diastolic blood pressure (DBP) was 98 mmHg prior to the stroke.[7] Based on their results, the authors made new recommendations to administer antihypertensive medications to all women with systolic blood pressures above 155-160 mmHg, thereby influencing a change in management of acute-onset severe hypertension. While the underlying presumption is that antihypertensive treatment in a timely fashion will reduce maternal morbidity, there are no studies that have documented reductions in SMM after such timely treatment. Therefore, the primary aim of our study was to evaluate if timely treatment of severe maternal hypertension was associated with a reduction in SMM. Our secondary aim was to compare the demographic and clinical characteristics between women with severe hypertension with and without SMM.

MATERIALS AND METHODS

Under the Institutional Review Board-approved protocol (no. Pro00042637), we conducted a retrospective cohort study of all women with severe hypertension who delivered at a

large urban academic medical center between January 1, 2012 and June 30, 2014. This time period was chosen for consistency with our previous study on SMM.[3]

Potential cases of SMM were identified by the following five criteria: 1) International Classification of Diseases, Ninth Revision (ICD-9) codes for severe illness as identified by the Centers for Disease Control and Prevention[8]; 2) prolonged postpartum length of stay (≥ 4 days for vaginal delivery, ≥ 6 days for cesarean delivery); 3) hospital readmission within 30 days of discharge; 4) Intensive Care Unit (ICU) admission; and 5) transfusion of ≥ 4 units of packed red blood cells (pRBCs).[9] Each potential SMM case was then reviewed by a multidisciplinary team of specialists representing obstetrics and gynecology, maternal fetal medicine, neonatology, obstetric anesthesia, nursing and epidemiology. True SMM was determined by utilization of the Gold Standard Severe Maternal Morbidity Case Review Guidelines.[10, 11] Using these Guidelines, true SMMs were defined as obstetric hemorrhage (defined as transfusion with: ≥ 4 units of pRBCs; 2 units of pRBCs and 2 units of fresh frozen plasma; <4 units of blood products and evidence of pulmonary congestion that requires >1 dose of Lasix; 2-3 units of blood products and placement of uterine balloon or uterine compression sutures; uterine artery embolization; emergent or unplanned peripartum hysterectomy; return to operating room for any major procedure; or ICU admission for invasive monitoring or treatment), cardiomyopathy, arrhythmia, cerebrovascular event, eclampsia, complicated HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, disseminated intravascular coagulation, abruptio placenta, acute renal failure, acute liver failure, pulmonary edema, cesarean delivery complications and uncontrolled postpartum hypertension requiring intravenous antihypertensive requirement > 48hrs after delivery.[10, 11]

Severe hypertension was defined as at least two severe blood pressures (SBP ≥160 mmHg and/or DBP ≥110 mmHg) within 60 minutes.[12] Data abstracted on maternal hypertension included timing of all severe blood pressures and timing of administration of antihypertensive medications. The dose of each antihypertensive medication was determined to be appropriate or inappropriate for acute treatment as per ACOG recommendations.[5] The initial dosing of first-line antihypertensive medication was determined to be therapeutic for treatment of initial episode of severe hypertension if the subsequent SBP and DBP were less than 160 and 110 mmHg, respectively, and successive dosing was not required.

Antihypertensive treatment was determined to be timely or not timely, based on the ACOG and CMQCC definition of timely treatment, which is treatment with an antihypertensive medication within 60 minutes of confirmed severe hypertension.[5, 6] Accordingly, we defined not timely treatment as treatment delayed longer than one hour from confirmed severe hypertension, which included women who did not receive any treatment.

We also extracted data on demographics (age, race and ethnicity, body mass index (kg/m^2), insurance) and pregnancy characteristics (parity, plurality, estimated gestational age at delivery, timing and route of delivery) from the electronic medical records of women with severe hypertension.

Statistical methods used to evaluate demographic and clinical characteristics between the groups of severely hypertensive women with and without SMM included univariate analyses (χ^2 test, analysis of variance, t-test, Fischer's Exact test, Wilcoxon test) as appropriate to the distribution. We performed multivariate logistic regression, adjusting for maternal age, race/ethnicity, twin gestation and insurance type, to evaluate the association between timely

treatment and the occurrence of SMM. The significance (alpha) level was set at $p < 0.05$. All analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Between January 1, 2012 and June 30, 2014, there were 16,325 total deliveries from which we identified 465 women with severe hypertension confirmed within one hour. Of these, 29 women (6.2%) were determined to have true SMM. Eleven cases were excluded due to occurrence of SMM prior to diagnosis of severe hypertension, leaving 18 cases with true SMM following diagnosis of severe hypertension. Primary SMM diagnoses included eclampsia (n=5; 28%), complicated HELLP syndrome (n=3; 17%), postpartum hemorrhage (n=3; 17%), pulmonary edema (n=3; 17%), uncontrolled postpartum hypertension requiring acute antihypertensive treatment >48 hours after delivery (n=2; 11%) and cesarean delivery complications (n=2; 11%). Four patients had more than one SMM: 3 patients with HELLP syndrome (primary SMM) subsequently developed DIC and postpartum hemorrhage, requiring transfusion with ≥4 units of pRBCs. One patient with postpartum hemorrhage (primary SMM) also had uncontrolled postpartum hypertension requiring intravenous antihypertensive treatment >48 hours after delivery.

Table 1 compares demographic and pregnancy characteristics of the severely hypertensive women between those with and without SMM. Compared to women without SMM, women with SMM were significantly more likely to be ≥ 40 years old ($p= 0.01$) and to deliver before 37 weeks ($p< 0.001$). Of note, all women with SMM had cesarean deliveries compared to 52% of women without SMM ($p< 0.001$).

In comparing demographic and pregnancy characteristics of severely hypertensive women, those women who did not receive timely treatment were significantly more likely to be 40 years old or older ($p= 0.003$), have a multifetal gestation ($p= 0.03$), and have private insurance or self-pay (88% in not-timely vs. 80% in timely) ($p= 0.02$) compared to those women who received timely treatment (Table 2).

Fifty-six percent of women (n=262/465) received timely treatment within 60 minutes of confirmed diagnosis of severe hypertension while 44% of women (n=203/465) did not receive timely treatment. Of those women who received timely treatment, only 1.9% (5/262) had an SMM compared with 6.4% (13/203) of women who did not receive timely treatment ($p= 0.02$). Timely treatment was associated with a 72% reduction in relative odds of SMM (adjusted odds ratio = 0.28, 95% confidence limits 0.10 and 0.81, $p= 0.02$) (Table 3).

There was no significant difference in the median pre-treatment systolic blood pressures in women with and without SMM (Table 4). The majority of women were diagnosed with severe hypertension antepartum, regardless of whether they had an SMM. There were no significant differences in first-line medication used between the SMM and no SMM groups. The majority of women in both groups received appropriate dosage of initial medication. Women with SMM received a median of 5.5 doses of acute antihypertensive medications, compared to women without SMM who received 2 doses ($p<0.001$). Seventy-two percent of women with SMM were given ≥ 2 different antihypertensive medications vs. 36% of women without SMM ($p=0.002$). Among those women who received timely treatment, the initial drug dosing was therapeutic in achieving non-severe blood pressures in 60% and 62% of women with SMM and without SMM, respectively ($p=0.98$).

DISCUSSION

The overall rate of SMM in United States is estimated to be in 0.05-1.13% of all pregnancies.[10, 11] In our study of 465 women with severe hypertension, the SMM rate was 3.9%. More significantly, we now report that treatment of severe hypertension within 60 minutes of confirmed diagnosis was associated with a significant reduction in SMM. These data strongly support recent ACOG and CMQCC guidelines to treat women with severe hypertension with antihypertensive medications within 60 minutes of diagnosis.[5, 6]

It is noteworthy that there was no difference in the median pre-treatment systolic blood pressures (170 mmHg and 162 mmHg respectively), or in adequate response to initial treatment between women who did or did not develop SMM. This suggests that neither severity of initial blood pressures or initial response to treatment identifies women likely to develop SMM. However, women who developed SMM did require significantly more treatment doses and higher number of different medications than those women who did not develop SMM. These findings suggest that women who are at a higher risk of SMM have hypertension that is more difficult to treat but cannot be identified based on initial severity of severe hypertension or their response to initial treatment. Women with severe hypertension, therefore, require constant vigilance and timely treatment with antihypertensive medications to reduce their risk of SMM.

More recently, several studies have evaluated the implementation of checklist-based protocols for rapid treatment of severe hypertension.[13-15] One such study by Shields et al proposed the use of Maternal Early Warning Trigger Tool to improve timely assessment and treatment of patients with abnormal vital signs.[14] Implementing this tool in obstetric units of 6 hospitals in a large hospital system showed that standard surveillance and assessment was

associated with a significant reduction in SMM. While important, studies such as these only compared morbidity rates before and after the implementation of protocols.[13-15] Unlike our study, they did not evaluate patient-specific responses to rapid treatment of hypertension and thus were unable to determine if timely treatment of severe hypertension contributed to reduced SMM.

A unique strength of our study is that we specifically examined the association between timely treatment of severe maternal hypertension and reduction in SMM. In a previous study of more than 2000 women with severe hypertension, pertinent details including the timings of SMM and antihypertensive treatment were lacking, so determination of any effect of timing of treatment on incidence of SMM could not be made.[12] In contrast, by determining when the SMM occurred relative to treatment with antihypertensive medication, we were able to confirm that timely treatment with antihypertensive medication was associated with a reduction in SMM.

An unexpected finding in our study was that several of the SMMs were not typically expected in women with acute severe hypertension suggesting that women with severe hypertension have an increased risk of all-cause morbidity. For example, two women with acute severe hypertension underwent cesarean deliveries and had surgical complications (bowel injury and ligation of left inferior epigastric artery) as their SMMs. While surgical complications are not typically expected in women with severe hypertension, their risk for such complications are increased due to cesarean delivery. By showing that timely treatment of severe hypertension is associated with reduced morbidity, our results suggest that rapid treatment with antihypertensive medications may simply be a marker for good overall care, attributed to increased vigilance provided by healthcare providers.

Our study is not without limitations, one being the small number of cases of SMM. While we screened 16,325 deliveries and identified 465 women with severe hypertension, only 18 had SMM, which included eclampsia, postpartum hemorrhage, complicated HELLP syndrome, surgical complications and pulmonary edema. Another limitation of our study is its retrospective design. However, although a randomized control trial is considered an ideal study design, randomizing patients to study the association between timely treatment of severe maternal hypertension and SMM would be unethical.

In summary, in our study of large number of women with severe hypertension, antihypertensive treatment within 60 minutes of confirmed diagnosis was associated with a reduction in severe maternal morbidity. As there was no difference in the median pre-treatment systolic blood pressures between women with and without severe morbidity, our findings support current recommendations to treat all women with severe hypertension with antihypertensive medications in a timely fashion.[4-6]

Table 1: Maternal and pregnancy characteristics in women with severe hypertension with or without severe maternal morbidity (SMM)			
	SMM N=18	**No SMM N=447**	**P-value***
Maternal Age, y, mean ± SD	37 ± 8	34 ± 6	0.08
≥40, n (%)	7 (39%)	74 (19%)	0.01
Race/Ethnicity, N (%)			
White, Non-Latina	9 (50%)	182 (41%)	
Black, Non-Latina	5 (28%)	83 (19%)	
Latina	1 (6%)	91 (20%)	0.44
Asian	2 (11%)	77 (17%)	
Other/Unknown	1 (6%)	14 (3%)	
Insurance Type,† N (%)			
Private/Self Pay	13 (72%)	371 (84%)	0.20
Medicaid/Medicare	5 (28 %)	72 (16%)	
Parity, N (%)			
Nulliparous	14 (78%)	313 (70%)	0.48
Parous	4 (22%)	134 (30%)	
Gestational Age at Delivery, N (%)			
≥ 37 weeks	5 (28%)	270 (60%)	<.001
< 37 weeks	13 (72%)	177 (40%)	
Multifetal, N (%)	2 (11%)	50 (11%)	0.99
Body Mass Index, N (%)			
Ideal	2 (11%)	45 (10%)	
Overweight	8 (44%)	159 (36%)	0.71
Obese	8 (44%)	241 (54%)	

Mode of Delivery, N (%)			
Normal vaginal delivery	0 (0%)	199 (45%)	
Operative vaginal delivery	0 (0%)	16 (4%)	<.001
Primary Cesarean Delivery	15 (83%)	184 (41%)	
Repeat Cesarean Delivery	3 (17%)	48 (11%)	

Univariate analyses included χ^2 test, t-test, Fischer's Exact test, and Wilcoxon test as appropriate to the distribution.

* All table percentages were calculated excluding missing values

† Insurance missing in <1%

Table 2: Maternal and pregnancy characteristics in women with severe hypertension who received timely vs. not timely treatment			
	Timely treated N=262	**Not timely treated N=203**	**P-value***
Maternal Age ≥ 40, N (%)	34 (13%)	48 (24%)	0.003
Race/Ethnicity, N (%)			
White, Non-Latina	100 (38%)	91 (45%)	
Black, Non-Latina	51 (20%)	37 (18%)	
Latina	62 (24%)	30 (15%)	0.15
Asian	42 (16%)	37 (18%)	
Other/Unknown	7 (3%)	8 (4%)	
Insurance Type,† N (%)			
Medicaid/Medicare	53 (20%)	24 (12%)	0.02
Private/Self Pay	207 (80%)	177 (88%)	
Gestational Age at Delivery, N (%)			
≥ 37 weeks	158 (59%)	119 (58%)	0.81
< 37 weeks	104 (41%)	84 (42%)	
Multifetal, N (%)	22 (8%)	30 (15%)	0.03
Body Mass Index, N (%)			
Ideal	29 (11%)	18 (9%)	
Overweight	83 (32%)	84 (42%)	0.09
Obese	149 (57%)	100 (50%)	
Mode of Delivery, N (%)			
Normal vaginal delivery	128 (49%)	87 (43%)	0.20

Cesarean Delivery	134 (51%)	116 (57%)

Univariate analyses included χ^2 test, t-test, Fischer's Exact test, and Wilcoxon test as appropriate to the distribution.

* All table percentages were calculated excluding missing values

† Insurance missing in <1%

Table 3. Association between timely treatment of severe hypertension and severe maternal morbidity (SMM)						
	SMM N=18	**No SMM N=447**	**Unadjusted OR (95% Limits)**	**P-value**	**Adjusted† OR (95% Limits)**	**P-value**
Timely N=262	5‡ (1.9%)	257 (98.1%)	0.28 (0.10-0.81)	0.02	0.28 (0.09-0.82)	0.02
Not-Timely N=203	13§ (6.4%)	190 (93.6%)				

† Adjusted for age, race/ethnicity, twins, insurance

‡ SMMs included postpartum hemorrhage (n=1), HELLP syndrome complicated by disseminated intravascular coagulopathy (n=1), and pulmonary edema (n=3).

§ SMMs included eclampsia (n=5), postpartum hemorrhage (n=3), HELLP syndrome complicated by disseminated intravascular coagulopathy (n=2), cesarean complications of bowel injury and ligation of left inferior epigastric artery (n=2), and uncontrolled hypertension requiring acute antihypertensive treatment > 48 hours after delivery (n=1).

Odds Ratio Estimates and Wald Confidence Intervals			
Effect	**Estimate**	**95% CI**	**P-value**
Timely treatment: Yes vs No	0.277	(0.09, 0.82)	0.02
Race: Black vs Not Black	1.622	(0.52, 5.05)	0.40
Twins: Yes vs No	0.737	(0.15, 3.54)	0.70
Age: GE40 vs LT40	3.468	(1.21, 9.98)	0.02
Insurance: Gov't vs Private/Self Pay	2.706	(0.83, 8.85)	0.10

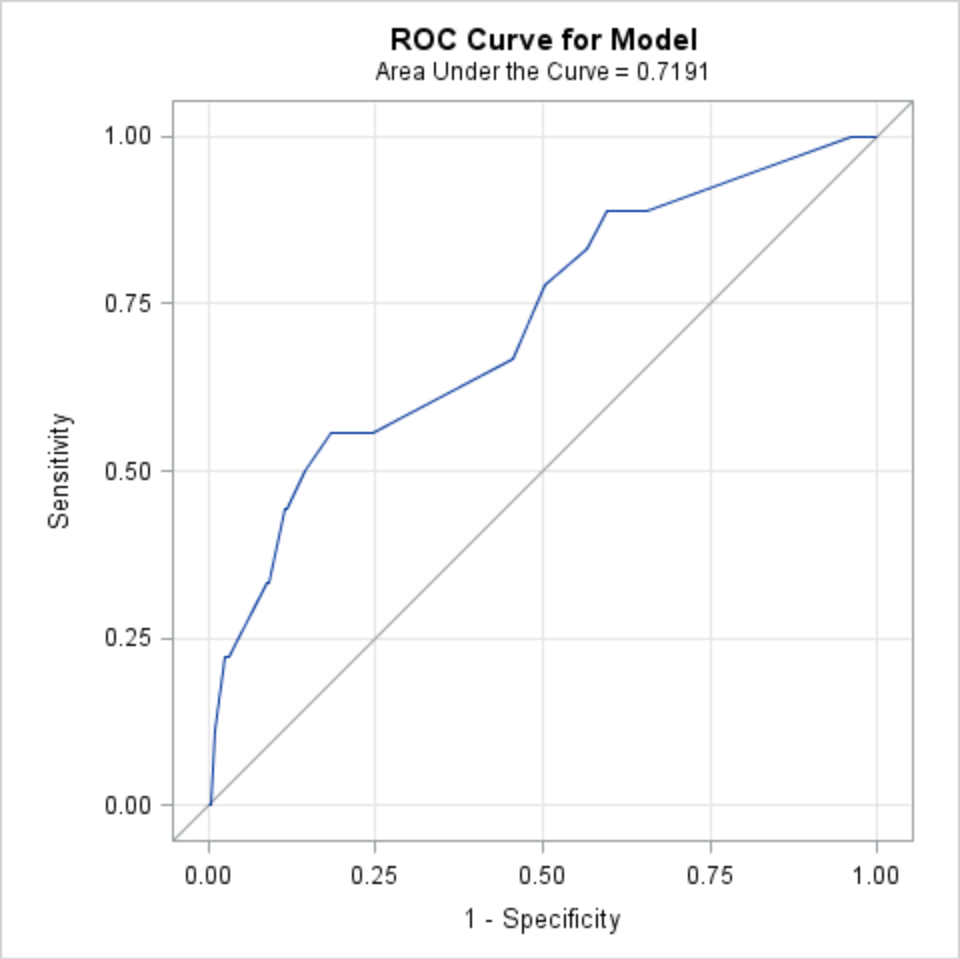
ROC Curve for Model
Area Under the Curve = 0.7191
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Table 4: Clinical characteristics of women with severe hypertension with or without severe maternal morbidity (SMM)

	SMM N=18	No SMM N=447	P-value*
Pre-treatment Blood Pressure, median (IQR)			
Systolic Blood Pressure	170 (22)	167 (13)	0.20
Diagnosis of Severe Hypertension, N (%)			
Antepartum	13 (72%)	362 (81%)	0.36
Postpartum	5 (28%)	85 (19%)	
Initial Drug Used,† N (%)			
IV hydralazine	14 (78%)	214 (48%)	
IV labetalol	2 (11%)	150 (34%)	0.10
PO labetalol	1 (6%)	45 (10%)	
PO nifedipine	1 (6%)	33 (8%)	
Appropriate Initial Dose Given, N (%)	15 (83%)	368 (83%)	0.99
Doses of Acute Antihypertensive given, median (IQR)	5.5 (15)	2 (3)	<0.001
Different Antihypertensive Medications used, N (%)			
≥ 2 medications	13 (72%)	142 (36%)	0.002

Univariate analyses included χ^2 test, t-test, Fischer's Exact test, and Wilcoxon test as appropriate to the distribution.

* All table percentages were calculated excluding missing values

Table 5: Clinical characteristics of women with severe hypertension who received timely vs. not timely treatment			
	Timely N=262	**Not Timely N=203**	**P-value***
Pre-treatment Blood Pressure, median (IQR)			
Systolic Blood Pressure	170 (17)	166 (8)	<0.001
Initial Drug Used, † N (%)			
IV hydralazine	144 (55%)	84 (42%)	<0.001
IV labetalol	108 (41%)	44 (22%)	
PO labetalol	1 (0.4%)	47 (24%)	
PO nifedipine	8 (2.6%)	24 (12%)	
Doses of Acute Antihypertensive given, median (IQR)	1(2)	1 (2)	<0.001
Different Antihypertensive Medications used, N (%)			
≥ 2 medications	56 (28%)	99 (38%)	0.03

Univariate analyses included χ^2 test, t-test, Fischer's Exact test, and Wilcoxon test as appropriate to the distribution.

* All table percentages were calculated excluding missing values

† Timely group missing 1 value (N=261). Not Timely group missing 4 values (N=199).

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