Early Standardized Treatment of Critical Blood Pressure Elevations is Associated
With a Reduction in Eclampsia and Severe Maternal Morbidity

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Short version of title

Standardized Treatment of Critical Blood Pressure
ABSTRACT

Background: Hypertensive disorders of pregnancy result in significant maternal morbidity and mortality. State and national guidelines have been proposed to increase treatment of patients with hypertensive emergencies or critically elevated blood pressures. There is limited data available to assess the impact of these recommendations on maternal morbidity.

Objective: The purpose of this prospective quality improvement project was to determine if maternal morbidity would be improved using a standardized approach for treatment of critically elevated blood pressures.

Study Design: Twenty-three hospitals participated in this project. Treatment recommendations included the use of an intravenous blood pressure medication and magnesium sulfate when there was a sustained blood pressure of ≥160 mmHg systolic and/or ≥110 mmHg diastolic. Compliance with the metric recommendations was monitored based on the number of patients treated with an intravenous blood pressure medication, use of magnesium sulfate, and if they received a timely postpartum follow-up appointment. The metric was scored as “all-or-none”, missing any of the three metric components was considered non-compliant. From January through June of 2015 baseline data was collected and hospitals were made aware that ongoing monitoring of compliance would begin in July of 2015 through June 2016. The primary outcomes were composite metric compliance, the incidence of eclampsia per 1,000 births and severe maternal morbidity.

Results: During the 18 months of this study there were 69,449 births. Within this population,
2,034 met criteria for a critically elevated blood pressure, preeclampsia or superimposed preeclampsia with severe features. Of this group, 1,520 had a sustained critical blood elevation. Initial compliance with treatment recommendations was low (50.5%) and increased to >90% after April 2016 (p<0.001). Compliance with utilization of intravenous blood pressure medication increased by 33.2%, from a baseline of 57.1% to 90.3% (p<0.01) during the last 6 months of monitoring. Compliance with utilization of magnesium sulfate increased by 10.8%, from a baseline of 85.4% to 96.2% (p<0.01). The incidence of eclampsia declined by 42.6% (1.15±0.15/1,000 to 0.62±0.09/1,000 births). Severe maternal morbidity decreased by 16.7% from 2.4±0.10% to 2.0±0.15% (p<0.01).

**Conclusion:** We noted three important findings: 1) compliance with state and national treatment guidelines is low without monitoring; 2) high levels of compliance can be achieved in a relatively short period of time; 3) early intervention with intravenous blood pressure medication and magnesium sulfate for verified sustained critical maternal blood pressures resulted in a significant reduction in the rate of eclampsia and severe maternal morbidity. The reduction in the rate of eclampsia could only partially be attributed to the increase in the use of magnesium sulfate, suggesting an additive or synergistic effect of the combined treatment of an antihypertensive medication and magnesium sulfate on the rate of eclampsia and severe maternal morbidity.

**Keywords:** blood pressure treatment, eclampsia, preeclampsia, severe maternal morbidity.
BACKGROUND AND OBJECTIVE

Globally, hypertensive disorders of pregnancy continue to be a significant contributor to maternal mortality and morbidity.\(^1\) While these adverse outcomes are more pronounced in developing nations, they continue to be one of the main contributors to maternal mortality and morbidity in the United States.\(^2\)\(^ ,\)\(^3\) In 2013, the American College of Obstetricians and Gynecologists (ACOG) published their Executive Summary on Hypertension in Pregnancy.\(^4\) This document redefined certain aspects of the definition of hypertensive disorders in pregnancy as well as treatment guidelines. The summary supported treatment guidelines for use of medication for hypertensive emergencies where systolic and/or diastolic blood pressure are above 160/110 mmHg. These recommendations were further refined in national guidelines (Council on Patient Safety in Women’s Health),\(^5\) and state toolkits from California\(^6\), New York\(^7\), and Florida.\(^8\) Both the national and state organizations took a more aggressive approach toward treatment of hypertensive emergencies or critical blood pressures by recommending that patients be acutely treated if blood pressure values were sustained, defined as persistent values greater or equal to 15 minutes apart. They also recommended that these patient be treated with magnesium sulfate for seizure prophylaxis. In an attempt to reduce postpartum morbidity, early follow-up was likewise recommended.

As part of the California Maternal Quality Care Collaborative (CMQCC) toolkit implementation, a group of 24 hospitals, comprising both academic medical centers and community hospitals, agreed to trial the toolkit at their institutions. These 24 hospitals were collectively known as the CMQCC Preeclampsia Collaborative. One component of the collaborative was to test their ability to follow the toolkit guidelines for blood pressure verification and treatment of a
confirmed critical blood pressure within 1 hour. Their data suggested that only 41% of sites met this goal. This hospital collaborative went on to show that improving the number of patients treated within 1 hour was associated with a reduction in severe maternal morbidity. Similarly, treating critical blood pressures as part of a maternal early warning trigger (MEWT) tool resulted in a significant reduction in the rate of eclampsia. The purpose of this investigation was to determine if using key elements from CMQCC and the Council on Safety in Women’s Health guidelines would reduce the incidence of eclampsia and severe maternal morbidity within a large group of community hospitals. We focused on three key elements: 1) treatment of critically elevated blood pressures within one hour of verification; 2) use of magnesium sulfate in the presence of critically elevated blood pressures regardless if other criteria for preeclampsia were present; and 3) early postpartum follow-up assessment.

MATERIALS AND METHODS

This study used de-identified and aggregate data as part of a clinical patient safety monitoring program which was approved by Dignity Health’s System Institutional Review Board. In May of 2014, the 23 hospitals that are included in this study were provided with recommendations for the management and treatment of preeclampsia and critically elevated blood pressures, that were consistent with CMQCC guidelines designed to reduce maternal morbidity and mortality. Detailed monitoring of utilization of these recommendations was not carried-out at that time. During this same time period we initiated a pilot project at six hospitals, not include in this report, to test a maternal early warning trigger (MEWT) tool. The MEWT tool had recommendations for treatment of critically elevated blood pressures that were identical to those
evaluated in this project. Data from the MEWT trial sites suggested that the use of these recommendations was associated with a significant reduction in the rate of eclampsia. Similar to the approach that we took in our MEWT trial, patients with blood pressures that were elevated ≥ 160 mmHg systolic and/or ≥ 110 mmHg diastolic, were requested to have the blood pressure verified within 15-20 minutes. If the blood pressure elevations were sustained, it was considered a critical blood pressure and treatment with intravenous hydralazine or labetalol using a standard treatment algorithm was recommended.\textsuperscript{6,7,10} Blood pressures were rechecked prior to medication administration and if less than 160 mmHg systolic and 110 mmHg diastolic, antihypertensive medication was not administered unless a critical value was reached later in the course of the patient’s hospitalization. All patients meeting blood pressure criteria, regardless of the underlying cause of their hypertension, were expected to be treated with magnesium sulfate. Patients with preeclampsia with severe features or superimposed preeclampsia with severe features were also treated with magnesium sulfate per ACOG guidelines.\textsuperscript{4} Patients with preeclampsia without severe features could be treated with magnesium sulfate at the discretion of their physician. The final aspect of the process was to make sure all postpartum patients with a diagnosis of a hypertensive disorder of pregnancy were seen within two weeks of discharge if they had a hypertension diagnosis, or within one week postpartum if they required antihypertensive medication during their admission. Retrospective baseline data was collected from January 2015 to June 2015 to determine baseline compliance with the three metric components (blood pressure treatment, magnesium sulfate treatment, and follow-up guidelines). During this same time period from January to June 2015, hospitals were notified that monitoring of compliance and outcomes monitoring were going to begin in July of 2015. Educational presentations were made to all of the Obstetrics and Gynecology departments through the
hospital system’s annual perinatal meeting, monthly perinatal safety meetings, and webinar presentations. Monitoring of compliance began prospectively in July of 2015 and was continued for 1 year. Monitoring was divided into two time frames, each six months in duration. The 23 hospitals included, vary in annual delivery volume from 140 to nearly 5000 births. Data was prospectively collected at each hospital and collated monthly at the central perinatal safety office. Compliance for an individual case was rated as “all-or-none”, based on the utilization of all elements or absence of one or more of the three elements being monitored. For example, if a patient received magnesium but not antihypertensive medication if indicated, the case would be considered non-compliant. Similarly, if postpartum follow-up was not made in the specified time period, the case would be rated as non-compliant. System and individual hospital compliance status were presented in monthly perinatal safety web-based meetings. Primary outcome data were the rates of eclampsia per 1,000 births, the rate of Centers for Disease Control defined severe maternal morbidity (CDC-SMM) per 100 births\textsuperscript{11}, and overall compliance with the “all-or-none” metric. Three time periods were used for analysis: 1) baseline, from January to June 2015; 2) monitoring phase I, July 2015 through December 2015; and 3) monitoring phase II, January-June 2016. To establish a benchmark for evaluating data from the baseline time period, rates of CDC-SMM and the frequency of eclampsia were calculated from data collect from the preceding two years (2013-2014) and used for comparison.

Data were analyzed by comparing differences between independent populations using the online statistical analysis tool (Vassarstats.net; Richard Lowry, MD, Vassar College, Poughkeepsie, NY). Confidence intervals (90\textsuperscript{th} centile) were calculated using the online statistical analysis tool
RESULTS

During the 18 months of this project, there were a total of 69,449 births. Of these, 2,034 met criteria for treatment with magnesium sulfate. Blood pressure was not sustained in 514 patients (25.3%) and they did not require treatment with an antihypertensive medication (Table 1). The average pretreatment systolic blood pressure was 172.9 ± 14.0 mmHg (range 138-258 mmHg) and the average pretreatment diastolic pressure was 102.3 ± 13.9 mmHg (range 71-153 mmHg).

Isolated systolic blood pressure was more frequently elevated, noted in 75.8% of cases while isolated diastolic blood pressure was infrequent, noted in only 5.3% of cases. The combination of elevated systolic and diastolic blood pressure was noted in 18.9% of cases. As noted above, treatment with magnesium sulfate was recommended for all patients meeting blood pressure criteria as well as those that had other criteria of preeclampsia with severe features or superimposed preeclampsia with severe features. The rate of appropriate magnesium sulfate utilization increased by 10.9%, from 85.4% of cases during the baseline time period, to 92.0% in phase I of monitoring, and to 96.2% during phase II of monitoring (Table 1, p<0.01). A total of 1520 (74.7%) of patients had a sustained blood pressure elevation requiring treatment with an antihypertensive medication. At baseline, non-utilization of an antihypertensive agent was the most common reason for non-compliance, noted in 42.9% of cases. During the course of the study, the rate of acute blood pressure treatment for critical blood pressures increased by 33.2%, from a baseline rate of 56.9% of cases, to 79.2% during phase I of monitoring, to 90.2% during the 6 months of phase II monitoring (Table 1, p<01). Compliance with all three metric components increased from 50.5% at baseline to an average of 88.5% during phase II of
monitoring (p<0.01, Table 1). During the last three months of phase II monitoring the rate of compliance increased to 92.8%. Over the course of the project there was a significant shift in the preference of blood pressure medications used. During the baseline time period intravenous labetalol was the most frequent antihypertensive agent used (44.2%) while hydralazine was utilized slightly less frequently (38.6%). During phase II of monitoring the rate of hydralazine use had declined to 26.0% of cases and labetalol use increased to 63.8% of cases (p<0.01, Table 1).

During the years 2013-2014, there were a total of 95,393 deliveries and a total of 110 cases of eclampsia or 1.15 ± 0.15/1,000 births. During the 6-month baseline time period, when resources were available and recommendations for treatment were in place but monitoring of compliance was not yet occurring, the rate of eclampsia remained unchanged at 1.16 ± 0.12/1,000 births. After the initiation of monitoring, the rate of eclampsia decreased to 0.90 ± 0.10/1,000 births in phase I of monitoring. During phase II of monitoring, the rate of eclampsia had decreased by a total of 42.6% relative to 2013 through the baseline time period, to a rate of 0.62 ± 0.09/1,000 births (p=0.02, Figure 1). The rate of severe maternal morbidity was not different between years 2013-2014 and the baseline time period, 2.4 ± 0.08% and 2.4 ± 0.10% respectively. The rate of CDC-SMM declined by 16.7% between 2013 through the baseline time period and phase II of monitoring (2.4 ± 0.10% v. 2.0 ± 0.15%, p<0.01, Figure 1). Similarly, the rate of severe maternal morbidity in the group of 2,034 patients with a diagnosis of critical blood pressure elevations, preeclampsia with severe features, or superimposed preeclampsia severe features decreased by 28.5%, from a rate of 10.5 ± 2.0% at baseline to 7.5 ± 1.5% during phase II of monitoring (p<0.05). When the number of eclampsia patients were removed from the analysis the rate of
CDC-SMM was still a significantly reduced, p<0.01.

During course of the study there was a modest increase in the rate of spontaneous vaginal delivery (63.5% to 64.7%, p<0.01) and a decrease in the rate of operative vaginal deliveries (4.1% to 3.1%, p<0.01), while total cesarean sections (32.4% to 32.1%) and primary cesarean section rates (16.4% and 16.1%) remained unchanged (p=0.5 and p=0.3 respectively. There was no change in the rate of NICU admission or NICU admissions for infants with birth weights of greater than 2,500 grams (p=0.24 and p=0.16 respectively).

**Comment**

The primary goal of this project was to determine if using a relatively simple approach to management of critically elevated blood pressures would result in a measurable reduction in key maternal outcome measures. This management approach is consistent with recent recommendations from CMQCC, the National Council for Patient Safety in Women’s Health and other state organizations. We noted that both the rate of eclampsia, one of the most significant complications of hypertensive disorders of pregnancy, and the rate of severe maternal morbidity were reduced. The reduction in eclampsia was similar to our previous report using the same treatment algorithm that was a component of our maternal early warning trigger tool. The reduction in the rate CDC-SMM remained when eclampsia is removed from the calculation, suggesting that the increase in utilization of magnesium sulfate and treatment of critically elevated blood pressures resulted in other improvements in maternal outcomes. These findings are consistent with data, albeit at a different magnitude, from developing countries where the improvements in maternal mortality in patients with hypertensive disorders of pregnancy can
only partially be attributed to the use of magnesium sulfate.\(^\text{12}\)

Prior to the recently revised recommendations for the treatment of hypertensive disorders of pregnancy from state and national organizations, the rate of maternal mortality related to hypertensive disorders of pregnancy has not changed in over 20 years.\(^\text{3,13,14}\) In an effort to change this trend, ACOG\(^4\), CMQCC\(^6\), New York\(^7\), Florida\(^8\), and the Counsel for Patient Safety in Women’s Health\(^5\) have emphasized that pregnant women should have acute blood pressure treatment, and magnesium sulfate, if they meet the criteria for critical blood pressure elevation defined as a sustained elevation \(\geq 160\) mmHg and/or \(\geq 110\) mmHg diastolic. These blood pressure values were primarily chosen as they corresponded to predicted reductions in incidence of maternal stroke.\(^\text{15}\) However, the rate of severe maternal morbidity in patients with critical blood pressure elevation is high, 10.5% in this study. Kilpatrick et al\(^\text{16}\) noted a similar high rate of severe maternal morbidity (8.8%) in another patient population primarily defined by critical blood pressure elevation. Our data suggest that combined treatment with magnesium sulfate and intravenous blood pressure medication reduces the rate of severe morbidity and that the reduction in severe morbidity persisted after excluding cases of eclampsia from the calculation of CDC-SMM.

During the course of the study there was an increase in the number of patients that met criteria for treatment with magnesium sulfate. The exact cause of this change is not clear, but may reflect an increased recognition patients meeting criteria for preeclampsia with severe features. Of those meeting criteria for treatment with magnesium sulfate we noted a modest, 10.8% increase in the use of magnesium sulfate relative to the 33.2% increase in the use of a blood pressure
medication. The modest increase in the use of magnesium in this at risk population in phase II of monitoring would have expected to produced about a 17% reduction in eclampsia\textsuperscript{17} and not the 42.6% reduction we noted. While this study was not designed to evaluate this finding it would suggest that the combination of magnesium sulfate and antihypertension treatment is more effective than magnesium sulfate alone, with an estimated number needed to treat of 29 to prevent each case of eclampsia. Although recommendations for treatment and follow-up had been recommended in our hospitals based on the state and national recommendations and in cases of preeclampsia by ACOG\textsuperscript{18} the number of patient’s receiving care consistent with these recommendations was low, 50.5% at baseline. This was consistent previous findings from the CMQCC Preeclampsia Collaborative.\textsuperscript{9} After notifying all facilities that monitoring was going to take place as well as providing staff and physician education, compliance with all three metrics increased to over 90% in less than 1 year. These findings suggest that ongoing monitoring of patient quality improvement measures and key elements of patient care are essential for success. These conclusions are consistent with the recent observation that merely producing a recommendation for treatment of a specific condition does not produce a change in outcome.\textsuperscript{19}

We noted that the blood pressure medication choice shifted during the course of the study from a relatively equal mix of intravenous labetalol and hydralazine to predominantly intravenous labetalol. Although specific data related to this shift was not recorded, many of the hospitals could not initially use intravenous labetalol on their labor and delivery units until they had changed hospital policies allowing the use of labetalol outside of the intensive care units or telemetry units. This should be a priority at centers attempting to change their acute management of patient with critical blood pressures.
Our study has a number of key strengths but is also not without limitations. The largest strengths of our study were the size of the patient population (nearly 70,000), the consistent treatment approach across all 23 hospitals, and predefined outcome parameters. Ideally, the interventions tested here would have been part of a large randomized control trial. The disadvantages of this approach are cost and logistics of such a large study. Further, it is unlikely that intervention study in the United States with close to 70,000 patients will occur using another format, particularly in such a timely manner. The use of a prospective quality improvement process, while not as robust at a randomized controlled trial, offers the opportunity to rapidly test an intervention strategy in a large cohort with relatively rapid assessment of results. Additional limitations of this large project were related to data collection. While we prospectively collected data on key maternal interventions we were limited to predefined coded data for the collection of outcome measures and did not have detailed patient level information such a magnesium toxicity or gestational age at birth. In this study, we requested that blood be lowered and maintained below the threshold of 160/110 mmHg. Future investigations may want to focus on the ideal post-therapy blood pressure goal and determine if an ideal threshold can be identified that maximizes maternal and neonatal outcomes.

In summary, we noted significant improvements in the rate of eclampsia and severe maternal morbidity with the use of a simple intervention strategy related to blood pressure treatment and the use of magnesium sulfate. These data strongly support recent changes to state and national guidelines for treatment of patients with critical blood pressure elevations in pregnancy. This study was carried out in a large group of community hospitals with annual birth
volumes between 140 to nearly 5,000, suggesting that the intervention and outcomes noted here are likely applicable to most maternity units within the United States or similar health care systems.


6. DRUZIN ML, SHIELDS LE, PETERSON NL, CAPE V et al. Preeclampsia Toolkit: Improving Health Care Response to Preeclampsia California Maternal Quality Care Collaborative ToolKit to Transform Maternity Care); Developed under contract #11-10006 with the
7. New York State Department of HEALTH. Hypertensive Disorders in Pregnancy.


### Table 1. Population Characteristics and Outcome Data.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Monitoring Phase I</th>
<th>Monitoring Phase II</th>
<th>Monitoring N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deliveries:</td>
<td>22,506</td>
<td>24,409</td>
<td>22,534</td>
<td>69,449</td>
</tr>
<tr>
<td>Met criteria for criteria for treatment with magnesium sulfate:</td>
<td>589 (2.6%)</td>
<td>646 (2.6%)</td>
<td>799 (3.5%)</td>
<td>2,034 (2.9%)</td>
</tr>
<tr>
<td>Appropriately Treated with Magnesium Sulfate:</td>
<td>503 (85.4%)</td>
<td>597 (92.0%)</td>
<td>769 (96.2%)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Met criteria for acute blood pressure treatment:</td>
<td>504 (2.2%)</td>
<td>490 (2.0%)</td>
<td>526 (2.3%)</td>
<td>p=0.5</td>
</tr>
<tr>
<td>Appropriately treatment with Hypertensive medication:</td>
<td>287 (56.9%)</td>
<td>388 (79.2%)</td>
<td>474 (90.1%)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Blood pressure medication used:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Labetalol</td>
<td>44.2%</td>
<td>53.8%</td>
<td>63.8%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>- Hydralazine</td>
<td>38.6%</td>
<td>30.2%</td>
<td>26.0%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>- Oral Labetalol or Nifedipine</td>
<td>15.9%</td>
<td>16.0%</td>
<td>10.2%</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>
Figure 1. Rate of eclampsia per 1,000 births and rate of CDC-defined severe maternal morbidity (CDC-SMM) per 100 births.