COMMITTEE REPORT

Committee report on cerebrovascular disorders, including eclampsia and emergency medical services, of the Japan Society for the Study of Hypertension in Pregnancy

Yoshikatsu Suzuki1, Tomoko Adachi2, Yasumasa Ohno3, Hideo Matsuda4, Katsuhiko Naruse5, Hirohito Metoki6, Yuichiro Nakai7, Osamu Nakamoto8, Kazushi Watanabe9, Akihide Ohkuchi10, Tamao Yamamoto11

1Nagoya City West Medical Center, 2Aiiku Hospital, Maternal and Child Health Care Center, 3Ohno Ladies Clinic, 4Matsuda Perinatal Clinic, 5Nara Medical University, 6Tohoku University Graduate School of Medicine, 7Kawasaki Medical School Hospital, 8Osaka City General Hospital, 9Aichi Medical University School, 10Jichi Medical University School of Medicine, 11Department of Pharmacology Nagoya City University

This is the report of the Committee on cerebrovascular disorders, including eclampsia and emergency medical services, of the Japan Society for the Study of Hypertension in Pregnancy (JSSHP). Based on blood pressure (BP) analyses of eclamptic patients, it was concluded that BP variability was important for the onset of eclampsia. Furthermore, the Committee established guidelines for antihypertensive treatment that recommend a sliding scale of antihypertensive drug administration for hypertensive emergencies during both antepartum and postpartum periods.

Foreword

In 2010, the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) established a committee to discuss cerebrovascular disorders including eclampsia. The results are presented in this paper.

Committee activity

First meeting: December 4, 2010 (Okayama)
Second meeting: February 5, 2011 (Nagoya)
Third meeting: June 18, 2011 (Nagoya)
Fourth meeting: September 10, 2011 (Nagoya)
Fifth meeting: January 8, 2012 (Nagoya)

Main study contents

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2. Case analysis examination of the pathogenetic mechanism of eclampsia by Y. Suzuki and K. Watanabe

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4. Association between ambulatory blood pressure monitoring (ABPM), home blood pressure monitoring (HBPM) and cerebrovascular disorders by H. Metoki
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Results

1. Epidemiological study of eclampsia and cerebrovascular disorders

1) Examination of the onset of eclampsia using the perinatal database assembled by the Perinatal Committee of the JSOG

Of the 330,399 deliveries registered in the perinatal database assembled by the Perinatal Committee of JSOG from 2005 through 2009, there were 246 eclamptic cases (0.07%) available for analysis, and 4 cases of maternal mortality. The rate of primipara was 81.3%. The majority of eclamptic patients were delivered after 34 weeks of gestation, most often between 40–41 weeks of gestation. Approximately 5–10 patients developed eclampsia with hypertension and severe proteinuria during each of these two gestational weeks of gestation. In contrast, number of patients who developed eclampsia with only hypertension increased rapidly after 34 weeks of gestation (Figure 1). It was suggested that patients with preeclampsia developed eclampsia throughout the pregnancy after 22 weeks of gestation, while the majority of patients with gestational hypertension developed eclampsia after 34 weeks of gestation.\(^1\)

2) Investigation of the present situation regarding cerebrovascular disorders of pregnant women in Aichi Prefecture

The first large-scale investigation was conducted between 2005 and 2009 in primary care hospitals and high-level medical hospitals of Aichi Prefecture, Japan (AICHI DATA). Financial support was provided by the Perinatal Care Association of the Aichi prefectural government. Questionnaire surveys about cerebrovascular disorders of pregnant and postpartum women were conducted for all obstetric units in Aichi Prefecture (100% response rate in 2007 and 2010). The total number of deliveries between 2005 and 2009 was 322,599.

A total of 126 women (0.04%) developed eclampsia. Twenty-one women developed eclampsia during pregnancy (antepartum), 50 during labor (intrapartum), and 55 during puerperium (postpartum). Only one of the 126 women developed sequelae.

Twenty-six women (0.008%) developed cerebrovascular disorders: 14 had a good prognosis, 6 developed sequelae and there were 6 maternal deaths. The onset of cerebrovascular disorders occurred during pregnancy in 9 women, during labor in 3 women, and postpartum in 14 women. The causes were hypertensive cerebral hemorrhage in 8 women, subarachnoid hemorrhage in 5, Moyamoya disease in 3, cerebral infarction in 4, cerebral venous sinus thrombosis (CVT) in 2 and posterior reversible encephalopathy syndrome (PRES) in 2.\(^2\)

2. Mechanism of eclampsia based on case analysis

Eclampsia may involve a failure of cerebral autoregulation of blood flow with very high blood pressure (BP). There was a sudden and severe rise in BP [an increase of more than 30 mmHg in systolic BP (SBP) or more than 15 mmHg diastolic BP (DBP)] in 10 cases, when BP was measured during routine prenatal care and just before the onset of eclampsia in 11 eclamptic women.

Changes in BP were measured frequently in 5 cases for two days before onset of eclampsia compared with preeclamptic women who were managed similarly and did not develop eclampsia: (1) An increased ratio in BP, (2) BP variability (\(\Delta\)BP = maximum BP - average BP).

The increase in BP was more than 30 mmHg in SBP and 15 mmHg in DBP in all cases. A BP was more than 30 mmHg in SBP and more than 15 mmHg in DBP in most of the eclampsia cases (4 of 5 cases), while none of the patients in the non-eclamptic but preeclamptic group met these criteria.\(^3\) These studies could not support that a BP increase over 30/15 mmHg could help to detect and manage eclampsia, and further evaluation is required (Figure 2).\(^3\)

These results suggest that not only a sudden rise in BP, but also severe BP variability, was associated with the

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**Figure 1.** Delivery weeks for women with eclampsia.\(^1\)

*: indicates maternal death.
onset of eclampsia.

3. Labor onset hypertension (LOH) and intrapartum eclampsia

SBP changes during delivery were measured in 1,014 normotensive pregnant women. When cervical os was dilated more than 5 cm during the first stage of labor, 761 women (75%) were normotensive (SBP < 140 mmHg), 121 (12%) had mild LOH (SBP, 140–150 mmHg), 65 (6%) had moderate LOH (SBP, 150–160 mmHg) and 66 (7%) had severe LOH (SBP ≥160 mmHg).

The frequency of eclampsia was 0.04% in AICHI DATA, and that of intrapartum eclampsia was 0.02%. Based on the hypothesis that LOH induces intrapartum eclampsia, it is speculated that intrapartum eclampsia develops in one of 350 women with LOH. It is suggested that intrapartum eclampsia might be prevented by the detection and antihypertensive treatment of LOH (unpublished data by Ohno).

4. HBPM and ABPM for eclampsia

Both HBPM and ABPM are available for exclusion of white coat hypertension. ABPM enables detection of masked hypertension, such as morning surge, midnight hypertension and stress-induced hypertension, by evaluating BP fluctuations (circadian rhythm) (Figure 3). Although ABPM is expected to be useful for hypertension during pregnancy, its use in pregnant women is not established currently.

HBPM has advantages over ABPM because it can eliminate observer bias and the white coat effect by measuring BP under the same conditions. However, use of HBPM has not been established for pregnant women.

5. Antihypertensive treatment in pregnant and postpartum women

Nifedipine and labetalol had been contraindicated in pregnant women, and nicardipine had been contraindicated for acute cerebral hemorrhage. The Ministry of Health, Labour and Welfare permitted their use in June 2011.

Representative antihypertensive treatments for
Table 1. Management of hypertension by antihypertensive treatment in ante, intra, and postpartum women

A. Management of severe hypertension in pregnancy induced hypertension (gestational hypertension, preeclampsia, superimposed preeclampsia)

Magnesium sulphate should be given intravenously in women with eclampsia or suspected eclampsia.

I) Oral administration (to keep BP 140–159/90–109 mmHg)

- first-line: methyldopa or labetalol
- second-line: long-acting oral nifedipine (after 20 weeks of gestation), hydralazine

II) Combination oral administration in uncontrolled severe hypertension by single-agent administration

- nifedipine and labetalol
- hydralazine and labetalol
- hydralazine and methyldopa

III) Intravenous administration in women with eclampsia, suspected eclampsia, HELLP syndrome, uncontrolled severe hypertension, or severe postpartum hypertension

- nicardipine (continuous intravenous infusion using syringe pump)
- hydralazine (intravenous)
- nitroglycerin (intravenous or continuous intravenous infusion using syringe pump)

B. Management of pregnancy with chronic hypertension

- methyldopa (oral), hydralazine (oral), or labetalol (oral)

Table 2. Intravenous administration of antihypertensive agent in pregnant women

- Intravenous nicardipine administration using a sliding scale are recommended if systolic BP remains ≥ 160 mmHg and/or diastolic BP remains ≥ 110 mmHg with BP goal ranging from 140–159/90–100 mmHg.
- Nicardipine stock solution (1 mg/ml) is given intravenously with a syringe pump.
- Start with an initial dose of 0.5 mg/hr, and measure BP after 30 minutes. If BP can control within target ranges, measure BP every 60 minutes.
- If BP remains ≥ 160/110 mmHg, increase a dose by 0.5mg/hr to a maximum dose of 2 mg/hr. A dose of > 2 mg/hr should be given under a doctor’s instruction.
- If BP falls to < 140/90 mmHg, reduce a dose by 1 mg/hr.
- If BP falls to < 120/80 mmHg, stop nicardipine. Non-stress test is recommended for assessment of fetal condition. Measure BP after 30 minutes and if BP remains ≥ 160/110 mmHg, restart with a dose of 0.5 mg/hr.

Table 3. Intravenous administration of antihypertensive agent in postpartum women

- Intravenous nicardipine administration using a sliding scale are recommended if systolic BP remains ≥ 140 mmHg and/or diastolic BP remains ≥ 90 mmHg with BP goal < 140/90 mmHg.
- Nicardipine stock solution (1 mg/ml) is given intravenously with a syringe pump.
- Start with an initial dose of 1 mg/hr, and measure BP after 30 minutes. If BP can control within target ranges, measure BP every 60 minutes.
- If BP remains ≥ 140/90 mmHg, increase a dose by 1 mg/hr to a maximum dose of 6 mg/hr. A dose of > 6 mg/hr should be given under a doctor’s instruction.
- If BP falls below 120/70 mmHg, reduce a dose by 1 mg/hr.
- If BP falls below 110/60 mmHg, stop nicardipine. Measure BP after 30 minutes and if BP remains ≥ 140/90 mmHg, restart with a dose of 1 mg/hr.
- This administration is recommended during pregnancy (for example, after onset of eclampsia). Then, a precipitous fall in BP after antihypertensive treatment may impair uteroplacental perfusion resulting in fetal heart rate abnormalities. Continuous cardiotocogram monitoring should be done. Termination of pregnancy is considered.
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Recommendations for antihypertensive medications in pregnant women are similar to those for postpartum women. The non-stress test (NST) is recommended to assess fetal condition when maternal BP is less than 140/90 mmHg in pregnant women, because a dramatic decrease in maternal BP may impair uteroplacental perfusion. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARB) and diuretics, which are contraindicated in pregnant women, may be administered to postpartum women if necessary. Breast feeding is a necessary consideration in postpartum women.

In women with symptoms of eclampsia, uncontrollable severe hypertension or severe postpartum hypertension, or after onset of eclampsia, intravenous antihypertensive medications may be needed to immediately lower BP to the desired goal.

The use of a sliding scale is recommended in pregnant women (Table 2) and postpartum women (Table 3). Nicardipine stock solution (1 mg/ml) is given intravenously with a syringe pump at 0.5–2 mg/h for pregnant women to keep SBP at 140–159 mmHg and DBP at 90–100 mmHg, and at 1–6 mg/h for postpartum women to maintain SBP at < 140 mmHg and DBP at < 90 mmHg. This postpartum antihypertensive treatment is recommended for women who develop eclampsia, even during pregnancy. In this case, a precipitous fall in maternal BP after antihypertensive treatment may impair uteroplacental perfusion, resulting in fetal heart rate abnormalities. Continuous fetal heart rate monitoring is required and termination of pregnancy should be considered.

6. Analysis of cerebral hemorrhage based on precedents and issues arising from medical lawsuits

We searched decisions in a law information database by TKC Co., Ltd. using the keywords “pregnancy”, “delivery” and “cerebral hemorrhage”, and extracted six target cases. Two patients developed PIH before onset of labor, three patients had hypertension after onset of labor, and one patient had cerebral hemorrhage an hour after BP increase. One case was thought to be due to lack of treatment for PIH.

The judgments in these cases were generally appropriate, but some cases assigned responsibility based on an inadequate theory from a medical perspective. It was suggested that establishment of a compensation system for sequelae and clarification of limitations of the current medical system is required.

7. Other

We conducted a questionnaire survey of obstetricians and neurosurgeons in Nara Prefecture, Japan, regarding strokes in pregnant women. The rate was approximately 60% in hospitals where brain surgeons were resident. Obstetricians performed computed tomography (CT) on pregnant women with stroke, and patients were transported to the obstetrics department (not to neurosurgery) of the high-level medical hospital in Nara.

Conclusion

- By analyzing BP in eclamptic patients, we found that BP variability was important to the onset of eclampsia.
- Detection and management of LOH might prevent intrapartum eclampsia.
- It is hoped that assessment of ABPM and HBPM is established in pregnant women.
- According to guidelines for antihypertensive treatment, a sliding scale of antihypertensive administration for hypertensive emergencies is recommended during both the antepartum and postpartum periods.

References