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Eclampsia: Morbidity, Mortality, and Management

KJERSTI M. AAGAARD-TILLERY, MD, PhD* and MICHAEL A. BELFORT, MD, PhD*†

**Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah; and †St. Marks Hospital, HCA, Salt Lake City, Utah*

Introduction

Pre-eclampsia is a multisystem disorder of pregnancy and the puerperium, complicating approximately 6% to 8% of all pregnancies in developed nations.[1,2] Pre-eclampsia may be defined by the clinical diad of new onset hypertension (sitting blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) and proteinuria (≥1+ in a random urine sample or ≥300 mg in a 24-hour collection).[1] It may also be accompanied by clinical symptoms after 20 weeks' gestation. These include an unremitting headache, visual changes, right upper quadrant pain, midepigastric pain, nausea and vomiting, oliguria, and shortness of breath. Each of these symptoms herald potentially severe clinical manifestations, including intracerebral hemorrhage, hypertensive encephalopathy, hepatic involvement (including hematoma or capsular rupture), renal failure, and pulmonary edema.

Pre-eclampsia may be subdivided into 2 categories, mild and severe, by virtue of the severity of the hypertension and proteinuria, as well as by the presence of unremitting symptoms as a manifestation of other organ involvement. In the most recent publication of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, the previously used traditional defining criteria of edema (≥2+ pretibial, facial, or presacral edema) and proteinuria (mild identified as ≥300 mg in a 24-hour collection, severe as ≥5 g) in a 24-hour collection have been altered in the diagnosis and distinction of mild and severe forms of the disorder.[2] Alternatively, current guidelines suggest that "Proteinuria is defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen. This will usually correlate with 30 mg/dL ("1+ dipstick") or greater in a random urine determination with no evidence of urinary tract infection. However, because of the discrepancy between random protein determinations and 24-hour urine protein in pre-eclampsia (which may be either higher or lower), it is recommended that the diagnosis be based on a 24-hour urine if possible or a timed collection corrected for creatinine

Correspondence: Michael A. Belfort, MD, PhD, 1200 East 3900 South, Salt Lake City, UT 84124. E-mail: uvmbelfo@ihc.com

excretion, when a 24-hour specimen is not feasible. The following findings increase the certainty of the diagnosis of the pre-eclampsia syndrome. Proteinuria of 2.0 g or more in 24 hours (2+ or 3+ on qualitative examination). The proteinuria should occur for the first time in pregnancy and regress after delivery."[2]

Eclampsia was initially recognized centuries ago (ancient Egypt) as seizures occurring uniquely in the context of pregnancy, as they resolved with delivery. In contrast to the prevalence of pre-eclampsia, eclampsia remains relatively uncommon; this is especially true in developed countries. Currently, the incidence of eclampsia is estimated at a rate of 0.04% to 0.1% in the United States and United Kingdom.[3,4] In contrast, it is much higher in developing countries, with reported rates as great as 15%.[5–7] It is estimated that eclampsia is a factor in up to 10% of all maternal deaths in developed countries and accounts for around 50,000 maternal deaths per year worldwide.[4,5–7] Although this disparity is generally thought to be due to underdiagnosis and delayed treatment of pre-eclampsia, such an assumption remains unproven. In fact, although eclampsia has frequently been regarded as the natural end result of untreated pre-eclampsia (hence the nomenclature), accumulating evidence and expert opinion now question whether eclamptic seizures are but one of a number of clinical manifestations of severe pre-eclampsia. Because of this shift in paradigm, it becomes imperative to recognize that although the pathophysiology of pre-eclampsia and eclampsia share a common biologic basis, there likely exist differing thresholds in patients whom may ultimately seize if left undelivered and without prophylaxis. Understanding the probable genetic and resultant pathophysiologic basis underlying such a differential will be imperative to the ultimate elucidation of the etiology of pre-eclampsia.

To this end, it is essential to recognize that although the pathophysiology of pre-eclampsia remains poorly understood, advances in recent years have brought to light a number of molecular and biochemical events presumptively essential in establishing a functional uteroplacental circulation.[8,9] Suffice it to say, future efforts will likely focus on deepening our understanding of the essential conserved regulatory process(es) that are both necessary and sufficient for an "appropriate" degree of endovascular invasion, which itself is dependent on well-orchestrated and finely tuned modifications of the muscularis layer of the spiral arteries.[8–10]

In this review, we will alternatively focus our attention on a brief summary of the natural history and resultant wide-ranging clinical manifestations of severe pre-eclampsia, with an emphasis on discussing whether management strategies currently employed truly alter the natural course of these disorders. We then will review accepted management strategies and anticipated outcomes in the setting of eclampsia. At the completion, it is our intent that the reader should be left with an employable management schema to be used when faced with an eclamptic patient.

NATURAL HISTORY

Despite our limited understanding of the etiology of pre-eclampsia, knowledge of its natural history and pathophysiology allows us to adequately manage the condition.[11] Over the centuries, many diverse therapies have been employed (rightly or wrongly) to both prevent and cure eclampsia. These have included systemic (sedation with morphine and chloral hydrate, phlebotomy, gastric lavage, mastectomy, and renal decapsulation) as well as hormonal (oophorectomy) and neuronal (spinal tap) interventions.[12]

Pre-eclampsia–eclampsia is widely thought of as primarily a disease of the young primigravid; however, this assumption is confounded by the fact that most primigravid pregnancies occur in young women. When one considers additional confounders of race, parity, multiple gestation, familial inheritance patterning, and predisposing medical disorders such as essential hypertension and renal disease, it is unclear which characteristics are

clearly associated with pre-eclampsia.[13–16] There is still some debate with respect to attributable risk allocated to race and parity. In a multivariate analysis of pre-eclamptics in the U.S., African-American women were shown to have an increased risk for the development of pre-eclampsia–eclampsia independent of age and parity.[13] By contrast, secondary analysis from the NICHHD Maternal-Fetal Medicine Units Network low-risk aspirin prevention trial failed to demonstrate any increased risk of preeclampsia along racial groupings, but did recognize an association with parity.[14,15] Nevertheless, the data do support that eclampsia can be prevented by adequate obstetrical care and judicious indicated delivery, as eclampsia is predominantly a disease of lower socioeconomic status and the developing world, and maternal mortality appears to vary according to the quality of accessible health care.[4–7,17,18]

Eclampsia may occur at any point during the puerperium, although most seizures are observed either intrapartum or within 48 hours of delivery. Late postpartum eclampsia, ie, seizures developing greater than 48 hours but prior to 6 weeks' postpartum, may, however, account for up to 26% of all cases of eclampsia.[19] It is of interest to note that others have observed marked ethnic variation in the occurrence of late postpartum eclampsia, with reports of prevalence among Nigerian women exceeding 60%.[20] In addition to variations in the timing of onset with respect to the puerperium, eclampsia may present at varying gestational ages, with the majority reportedly occurring in the third trimester,[21] although infrequent, atypical eclampsia has been observed at <20 weeks gestation. In these instances, a diagnosis of molar pregnancy or hydropic degeneration of the placenta should be excluded.[21–23]

Prognosis

PERINATAL

Although the perinatal mortality and morbidity rate secondary to eclampsia are in large part a reflection of the gestational age and maternal condition, the primary risks to the fetus are abruption of the placenta or placental insufficiency, complications of prematurity secondary to indicated delivery at the extremes of gestational age, and hypoxia secondary to maternal convulsions.[24–27] A number of retrospective and prospective studies have assessed both short and long-term outcomes of infants of eclamptic mothers. Sibai et al followed 28 preterm infants and 14 full-term infants for up to 50 months.[24] The majority of the infants were small for gestational age or intrauterine growth restricted; however, by a mean of 20.6 months nearly all of the infants had appropriate growth velocity with respect to weight, length, and head circumference. In terms of long-term neurologic sequelae, these authors found that observed major deficits mirrored those anticipated in premature or anomalous infants born to noneclamptic women.[24] In a recently published cohort from Sweden, similar outcomes were observed. Of note, in these authors' study intervals, there were no differences in either maternal or perinatal outcomes over the time intervals examined (1973–1979, 1980–1989, and 1990–1999).[28] Similar findings have been observed in other retrospective analyses, with higher perinatal morbidity and mortality at the extremes of gestational age in developing nations.[29,30]

MATERNAL

As with perinatal mortality, a number of factors influence maternal outcome following onset of eclamptic seizures. The overall maternal death rate varies from 0.4% to as high as 7.2% in developed countries; in developing nations with limited patient access to tertiary medical centers, maternal mortality may exceed 25%.[5,6,27,31] In the largest single cohort examined to date, the authors reviewed 990 cases of eclampsia over a 22-year interval. Multiple factors were observed to increase the maternal mortality rate: maternal age, gestational age, medical comorbidities including pre-existing renal disease and

essential hypertension, and multiple gestation.[32] Other authors have noted similar risks, as well as an independent risk based on parity.[21,27,33–36]

The primary manifestations of eclampsia associated maternal morbidity result from seizure-induced aspiration, pulmonary edema, recurrent seizure activity, or neurologic sequelae. When one considers that eclampsia has long been appreciated to involve reversible cerebral edema and loss of cerebrovascular autoregulation,[37–39] it is perhaps not surprising that among those women who die within 48 hours of the sentinel eclamptic seizure, over half will manifest cerebral petechiae and intracranial hemorrhage.[40] In the past, it has generally been considered that 5% to 8% of eclamptic women will develop neurologic sequelae, including generalized weakness, aphasia, cortical blindness, psychosis, and coma with persistent vegetative state.[37–41] Although neuroimaging studies have not proven useful in the management of pre-eclampsia/eclampsia, such studies have provided an opportunity to characterize cerebral manifestations of eclamptic seizures.[38,39] Computed tomography (CT) and magnetic resonance imaging (MRI) of eclamptic women have consistently demonstrated transient cortical abnormalities, most consistent with diffuse cerebral edema.[38,39] However, given the prevalence of these findings with the relatively low incidence of persistent neurologic sequelae, it is unlikely that cortical edema begets the ultimate neuropathophysiologic morbidity among eclamptics. Moreover, as other authors have pointed out: "The mortality rate of eclamptic women has been affected most dramatically by reduction of iatrogenic complications resulting from overmedication and overzealous approaches to vaginal delivery…It is important to realize, however, that the greatest improvement in survival can be attributed not to what was done but, rather, to what was not done."[42] With this in mind, we will now move onto a discussion of currently employed management strategies for eclampsia, and we will mention the rationale of each agent with respect to the putative pathophysiologic process that the drug addresses.

Management

PREDICTION AND PROPHYLAXIS

As we have already discussed, onset of eclampsia is not predicted by maternal characteristics, gestational age, or antepartum status. Moreover, although most women may manifest antecedent symptoms prior to onset of seizure (~80%), including frontal or temporal headache and/or visual disturbance, a significant number will not.[7,42–44] When a clear association between hypertension and seizure activity has been sought, the magnitude and duration of blood pressure elevation been shown to be predictive of cerebrovascular accident, but not eclampsia per se. Indeed, retrospective studies from developed nations have shown that 20% to 38% of eclamptic patients have a maximal blood pressure of less than 140/90 mm Hg prior to their seizure.[6,33,36] In a review by Sibai et al[36] of 179 consecutive cases, the factors found to be at least partially responsible for failure to prevent eclampsia were: physician error (36%), magnesium failure (13%), late postpartum onset (12%), early onset (<21 weeks [3%]), abrupt onset (18%), and lack of prenatal care (19%).[15]

Due to our inability to consistently and successfully predict those who might have an eclamptic seizure, it has been the recommendation and practice of many to employ seizure prophylaxis for mild and severe pre-eclamptics (including hemolysis, elevated liver enzymes, and low platelet count [HELLP]), as well as those with gestational hypertension who manifest cerebral antecedent symptoms or persistently elevated blood pressures (greater than 160 systolic and 105 diastolic).[1,45–50] Over the last 30 years, there have been several trials looking at efficacy and safety of various neuroprophylactic agents. An overview of these trials

is as summarized in Table 1 and is briefly reviewed below.

Following the publication of the landmark $MgSO_4$ for Prevention of Eclampsia (Magpie) trial, there now exists international consensus that magnesium sulfate ($MgSO_4$) is the prophylactic agent of choice for pre-eclamptic women.[26] Although $MgSO_4$ has been used to treat eclampsia for over 75 years, it was not until the publication of the findings of the Magpie trial that $MgSO_4$ became broadly accepted as a reliable means for preventing eclampsia. In brief, this well-designed and executed randomized, controlled trial enrolled 10,141 women with pre-eclampsia through 175 secondary and tertiary facilities in 33 countries. Primary outcome analysis was designed to examine the efficacy of prophylactic treatment with $MgSO_4$ in the prevention of eclampsia, alongside fetal or infant death prior to hospital discharge. Secondary outcomes were measures of serious maternal morbidity (by a priori rather than ad hoc composite outcome), toxicity, and mortality; for women randomized before delivery, additional secondary outcomes were complications of labor and delivery and neonatal morbidity. In sum of their findings, there were significantly fewer eclamptic convulsions among women allocated $MgSO_4$ than among those allocated placebo, to the order of a 58% lower relative risk (95% confidence interval [CI] 40–71% reduction). This reduction represents an overall finding of 11 per 1000 fewer women allocated $MgSO_4$ having had an eclamptic seizure. It is of interest, in light of our prior observations regarding risk of eclampsia in developing nations, a priori designated subgroup analysis among the 1560 women from nations with low perinatal mortality rates revealed no maternal deaths. By contrast, maternal mortality was highest in countries with high perinatal mortality, albeit the relative reduction in risk was consistent. With respect to secondary outcome analyses, there were no statistically significant differences among treatment groups in measures of maternal and perinatal morbidity with the exception of an observed protective effect for placental abruption in the $MgSO_4$ treatment group. The Magpie study demonstrated improved efficacy for eclamptic seizure prophylaxis without significant difference in maternal, fetal, or perinatal morbidity.[26] These results supported the findings of others.[25]

TABLE 1. Therapy for the Prophylaxis and Treatment of Eclampsia

Trial	Therapy Group	Seizure *or* Recurrent Seizure (%)
Prophylaxis		
Magpie Trial[26]	$MgSO_4$	0.8
	Placebo	1.9
Coetzee et al[25]	$MgSO_4$	0.3
	Placebo	3.2
Lucas et al[54]	$MgSO_4$	0.0
	Phenytoin	0.9
Belfort et al[53]	$MgSO_4$	0.8
	Nimodipine	2.6
Treatment		
Eclampsia Trial Collaborative Group[55]	$MgSO_4$	13.2, 5.7
	Phenytoin	17.1
	Diazepam	27.9

Based on a number of hypothesized mechanisms of action of $MgSO_4$, other agents with perceived similar physiologic or pharmacologic effect have been studied. We will briefly review 2 of these trials as they may provide insight into the underlying pathophysiology of pre-eclampsia. To date, no alternate therapies have proven to be as effective as $MgSO_4$ with respect to seizure prophylaxis or superior in terms of any reduction in maternal morbidity or mortality.

Given a known cerebral vasodilator effect of magnesium sulfate, we and others hypothesized that agents with a selective ability to improve cerebral vascular perfusion (possibly reducing epileptogenic local ischemia) would prove to be superior to the magnesium ion in prophylaxis against eclamptic seizures.[51,52] This hypothesis led to an international, multicenter trial in which 1650 women with severe pre-eclampsia were randomized to receive either a calcium channel blocker with known selective cerebral

vasodilatory effects (nimodipine) or intravenous $MgSO_4$.[53] Contrary to expectations, $MgSO_4$ was found to be more effective than nimodipine for the prevention of eclampsia (7 of 831 [2.6%] versus 21 of 819 [0.8%], $P = 0.01$). Of interest is that not only was there a significantly lower rate of eclampsia in the $MgSO_4$ group, but that this effect was primarily exerted in the postpartum interval (0 of 831 versus 9 of 819, $P = 0.01$).

The lack of effectiveness of nimodipine in the prevention of eclamptic seizures is consistent with the notion that cerebral ischemia likely represents a secondary pathophysiologic finding among eclamptics, and cerebral vasospasm is not the inciting event. Along these lines, we have recently proposed that eclamptic seizures may result from alteration in cerebral perfusion pressure.[51–53] In our model, cerebral overperfusion is initially opposed by physiologic vasoconstriction at the level of the conducting arteries, i.e., the middle cerebral artery, in the brain. Thus, as cerebral perfusion pressure increases, vasoconstriction at the middle/posterior and anterior cerebral artery level increases in an effort to protect cerebral blood flow in the more sensitive and thin-walled distal arterioles and capillaries. However, with persistent hypertension and excessive cerebral perfusion pressure, the arteries of the diameter of the middle/posterior and anterior cerebral arteries are ultimately damaged by a process of barotrauma. This results in failure of regulation at this level and the development of breakthrough cerebral perfusion pressure with resultant hypertensive encephalopathy. The distal blood vessels are then exposed to excessive pressures, and vasogenic (and occasionally cytotoxic) cerebral edema occurs. If this is left unchecked, vasospasm and cerebral ischemia with hemorrhage can occur. This hypothesis allows for the presence of both hypertensive encephalopathy and cerebral ischemia in the same patient, and, thus, may explain the disparate findings reported by those studying cerebral imaging in pre-eclampsia and eclampsia.

With respect to other neuroleptic agents, the work of Lucas et al has demonstrated an advantage of $MgSO_4$ over phenytoin for the prevention of eclampsia.[54] In this well-designed study, 2138 pre-eclamptic women were randomized to receive either $MgSO_4$ or phenytoin upon diagnosis and admission.[54] Primary outcome analyses again examined risk of eclampsia among the treatment groups, with secondary outcome analyses looking at maternal and neonatal outcomes. Eclamptic seizures developed in 10 of 1089 women receiving phenytoin, as compared with the absolute effectiveness of $MgSO_4$ in the other 1049 women ($P = 0.004$). Maternal and neonatal outcomes were similar in both groups, and there were no significant differences in risk factors between the 2 treatment groups. This study formalized the retrospective analysis previously performed at this same institution.[27] At this juncture, it bears mention that, in 1955, Pritchard initiated a standardized treatment regimen for women with eclampsia utilizing $MgSO_4$ at Parkland Memorial Hospital. In the ensuing 50 years, the basic components of this regimen have been tested repeatedly; $MgSO_4$ persists in its superiority to all regimens tested to date.

TREATMENT OF RECURRENT SEIZURES

In the absence of either initial prophylaxis or prompt treatment with initial seizure, approximately 10% of eclamptic women will have recurrent seizures. In 1995, the Eclampsia Trial Collaborative Group reported their findings from an international, multicenter randomized controlled trial.[55] In this study, 1687 eclamptic women were randomly allocated to 2 treatment categories: $MgSO_4$ versus diazepam and $MgSO_4$ versus phenytoin. The study was designed to look at the recurrence of convulsions with maternal death as its primary outcome; secondary outcome analyses were reported for a range of maternal and perinatal complications. In sum of their findings, women allocated magnesium had a 52% lower incidence of recurrent convulsions as compared to those allocated diazepam (13.2% [60/453] versus

27.9% [126/452]); women allocated magnesium had a 67% lower risk of recurrent seizures than those receiving phenytoin (5.7% [22/388] versus 17.1% [66/ 387). Of importance to note, when comparing maternal and neonatal risks for respiratory complications, phenytoin was significantly more likely to be associated with adverse outcomes. Thus, women who received phenytoin were more likely to be admitted to an intensive care facility, develop pneumonia, and/or require ventilatory support than those having received $MgSO_4$. These findings led the authors of the study to conclude that: "There is now compelling evidence in favor of $MgSO_4$, rather than diazepam or phenytoin, for the treatment of eclampsia."[55]

IMMEDIATE MANAGEMENT

Customary Seizure Supportive Care

The tenets of basic support should be followed. Maintenance of oxygenation with exogenous oxygen and assessment with a pulse oximetry should be employed; airway support should be obtained only if absolutely indicated. Special attention may be paid to minimization of aspiration risk in the pregnant women by placement in the left lateral decubitus position and utilization of suction. Placement of padded bed rails and restraints will assist in avoiding injury. Initiation of $MgSO_4$ should immediately ensue, with plan for movement toward delivery.

Magnesium Sulfate

The most common $MgSO_4$ regimen is a loading dose of 4 to 6 g administered intravenously over 15 to 30 minutes, followed by 2 to 3 g/hr as a continuous infusion (Table 2). The maintenance phase is given only if a patellar reflex is present, respirations are greater than 12 per minute, and urine output exceeds 100 mL in 4 hours. Following serum magnesium levels is not required if the woman's clinical status is closely monitored for evidence of potential magnesium toxicity; however, many advocate ascertainment of initial empirically determined therapeutic levels 6 hours after load or with subsequent titration in dosing. Although there does not appear to be a clear threshold concentration for the prevention of refractory seizures, a range of 4.8 to 8.4

TABLE 2. Dosage of $MgSO_4$ and Other Neuroleptic Agents

Drug	Loading Dose	Maintenance Dose	Therapeutic Level (Measured 6 Hours After Load)
$MgSO_4$			
Continuous intravenous infusion	4–6 g over 15–30 mins; diluted in 100 to 150 mL of IV fluids	2 g/hr infusion	4–8 mEq/L*
Intramuscular injector	10 g of 50% $MgSO_4$ solution (5 g into each buttock)	5 g every 4 hrs	4–8 mEq/L*
Refractory seizures	Reload with 2 g IV, not to exceed 2 doses, over 10 mins in a 20% solution		
Phenytoin	1–1.5 g over 1 hr	Depending on serum level (usually 250–500 mg every 10–12 hrs IV or PO)	10–20 μg/mL
Diazepam	—	10 mg/hr infusion	—

* Not tested prospectively.

PO, by mouth; —, data not available.

mg/dL has been recommended.[56] If a patient develops signs of magnesium toxicity, the infusion should be stopped immediately. The patient can then be evaluated for respiratory compromise by examination and pulse oximetry; oxygen should be administered and a serum magnesium level obtained. In instances of magnesium toxicity, treatment with 10 mL of 10% calcium gluconate solution infused over 3 minutes should promptly ensue. If respiratory or cardiac arrest occurs, resuscitation should be emergently initiated.

Eclamptic seizures are almost always self-limiting and seldom last longer than 3 to 4 minutes. Although our neurology or emergency medicine colleagues may recommend or consider the use of alternative neuroleptic agents, it behooves us to recall that the obstetrical literature has shown that in the setting of eclampsia the administration of such agents is seldom necessary or appropriate.[27,43–55] In instances where $MgSO_4$ fails to control recurrent seizures, other agents may be used (Table 2). If muscular paralysis is necessitated, then it should be employed in conjunction with intubation and mechanical ventilation.

Contraindications to Magnesium Sulfate

Contraindications to magnesium are limited. These include myasthenia gravis and myocardial ischemia or infarct. With respect to the latter, magnesium can interact with other cardiovascular drugs (ie, calcium channel antagonists) to elicit arrhythmias or reduce myocardial contractility. In addition, given its renal excretion, magnesium should be administered cautiously to patient in renal failure secondary to the realized risk of cardio respiratory depression.

Fetal Monitoring

Continuous electronic fetal monitoring should be shortly initiated following maternal stabilization. Transient fetal bradycardia lasting at least 3 to 5 minutes is a common finding after an eclamptic seizure and *does not necessitate immediate delivery.* Moreover, resolution of maternal seizure activity is often associated with compensatory fetal tachycardia and even with transient fetal heart rate decelerations that typically resolve within 20 to 30 minutes.[57] Every attempt should be made to stabilize the mother and resuscitate the fetus in utero before preceding to an emergent, potentially compromising delivery.

Considerations Regarding Delivery

The only effective treatment of pre-eclampsia/eclampsia is delivery; however, immediate delivery does not necessitate emergent cesarean section. The decision of whether to proceed with cesarean section or induction of labor and attempted vaginal delivery should be individualized based on obstetrical factors predicting anticipated interval to delivery. These would include parity with prior obstetrical history, gestational age, Bishop score, fetal status, and presentation. It is interesting to note that although there is a well-substantiated trend toward expectant management of severe pre-eclampsia less than 32 to 34 weeks' gestation, the trials looking at this management precluded eclamptic women in their enrollment.[58,59] Thus, eclampsia remains a contraindication to expectant management. In administering anesthesia, neuraxial techniques (epidural, spinal) are preferable provided there are no contraindications and attention is paid to avoidance of fluid status in anticipation of the risk of volume overload and pulmonary edema.[60]

Invasive Monitoring

Although other investigators have previously recommended the use of invasive hemodynamic monitoring in managing eclampsia for the purpose of fluid management, there exists no published evidence that the use of invasive hemodynamic monitoring is indicated nor of proven benefit.[61,62]

ANTIHYPERTENSIVE THERAPY

Antihypertensive agents are frequently used for the control of hypertension in the setting of

pre-eclampsia and eclampsia. The primary goal of therapy is to prevent life-threatening clinical conditions such as hypertensive encephalopathy, acute left ventricular failure, acute aortic dissection, or potentiation of conditions characterized by high levels of circulating catecholamines. However, it is of note to recall that cerebral hemorrhage accounts for 15% to 20% of deaths from eclampsia and is often associated with significant elevation in blood pressure (≥170/120). For these reasons, antihypertensive agents are an essential part of the management of eclampsia if there is hypertension.

Most experts would recommend employment of antihypertensive therapy for sustained diastolic pressures of ≥105 to 110 mm Hg and systolic blood pressures of ≥160 mm Hg, albeit these thresholds have not been tested prospectively. Historically, the most commonly used drug is hydralazine. Although hydralazine may be administered either intravenously as a bolus or infusion, or intramuscularly, the pharmacokinetics suggest that intermittent bolus injections are preferable. Thus, the NIH Working Group on Hypertension recommends initial 5 mg intravenous (IV) push followed by 5 to 10 mg boluses after 20-minute intervals as indicated; however, if no success by 20 mg IV or 30 mg intramuscularly (IM) in total, another agent should be employed.[2] If given IM, 10 mg should be the initial dose. An alternate, and in our opinion preferable, first-line agent is the short-acting beta-blocker labetalol. Labetalol should be initiated at a 20 mg IV bolus. If the effect is suboptimal, 40 mg should be administered after 10 minutes and 80 mg every 10 minutes for 2 additional doses. No single dose should exceed 80 mg nor a maximum cumulative dose of 220 mg.[2] As with all beta-blockers, its use is contraindicated in asthmatics.

We employ labetalol as our first-line agent for 2 reasons. First, its predictability in its timing and response to escalating doses. Second, other investigators have shown in a retrospective analysis a higher risk of both maternal and fetal complications with hydralazine when directly compared with labetalol.[63] Although others have previously advocated the use of nifedipine at 10 mg orally, short-acting nifedipine is not approved by the Food and Drug Administration (FDA) for management of hypertension.[64]

In the rare instances of hypertensive crisis, either sodium nitroprusside (initial rate 0.25 mcg/kg/min to a maximum dose of 5 mcg/kg/min) or nitroglycerine (initial IV infusion rate of 5 mcg/min, titrated to effect every 3 to 5 minutes to a maximum dose of 100 mcg/min) is administered. It bears mention that each drug actually has its preferential clinical application. Thus, given the preferential action of nitroglycerin as a preferential venous dilator, it is the agent of choice in pre-eclampsia associated with pulmonary edema and for control of hypertension associated with tracheal manipulation. Potential adverse effects include headache, tachycardia, and methemoglobinemia. Due to its ability to increase cerebral blood flow and intracranial pressure, it is contraindicated in hypertensive encephalopathy. Alternatively, sodium nitroprusside is the agent of choice in hypertensive encephalopathy due to its ability to cause arterial and venous relaxation by impedance of influx and intracellular release of calcium. However, sodium nitroprusside is metabolized into thiocyanate; cyanide accumulation can occur in large dosages (>10 mcg/kg/min) or after prolonged administration (>48 hours); fetal toxicity may occur after as little as 4 hours of administration. If toxicity is suspected, 12.5 g of sodium thiosulfate in 50 mL of D5W over 10 minutes is the antedote.[2,65]

Summary

Patients with eclampsia are at risk for maternal and perinatal morbidity and mortality. However, in the hands of astute, informed, and experienced clinicians, the risks to both mother and fetus can be minimized. Efforts in coming years will continue to be focused on delineating underlying etiology and

pathophysiology, as well as reducing the prevalence and incidence of eclampsia in developing nations.

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