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Review Article

Eclampsia in the 21st Century: Paradigm Shift from Empirical Therapy with Magnesium Sulfate. Basic Science Synthesis vs. Current Who-Recommended Pharmacotherapeutic Practice

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Abstract

Pathophysiology of preeclampsia / eclampsia is not clearly understood and its management with WHO recommended mega-doses of intravenous magnesium sulfate appears empirical or experiential. A characteristic albumin-cytological dissociation prevails in the cerebrospinal fluid (CSF), indicating a pressure-related hyperpermeability rather than disruption of blood-brain barrier (BBB). Hypomagnesemia, absolute or relative, is not specific or unique to seizures of preeclampsia / eclampsia. Magnesium is regarded as ideal drug for managing eclampsia but does not guarantee control of convulsions in a significant fraction. The pharmacokinetics and pharmacodynamics of magnesium are only partially understood. Magnesium does not freely cross the intact BBB, reduces permeability of BBB following large exogenous doses given intravenously in diverse experimental circumstances, and has no 'central' anticonvulsant action. Magnesium in large doses depresses the skeletal neuromuscular junction while sparing autonomic innervation and all brain functions, occasionally inducing a pseudo-coma like condition with flaccid quadriparesis but without impairment of cognition or consciousness. Cerebral arteries and CSF maintain a much higher level of ionic magnesium than systemic arteries, indicating the operation of distinct systemic and CNS compartments of magnesium controlled meticulously for brain homeostasis. Failure of CSF magnesium levels to rise in correspondence with mega-doses given intravenously is the clearest evidence against a clinically significant functional disruption of the BBB. Higher levels of low molecular albumin and dextran in CSF indicate a hypertension-related hydrostatic pressure mediated hyperpermeability. Cytokines and TNF-α70 are generated by the brain immune system, govern neuronal plasticity, and their elevated levels in the CSF do not indicate physical BBB disruption. A magnesium-related cause-effect-adaptive pathophysiologic continuum prevails in preeclampsia and eclampsia. Relative decrease of magnesium in plasma or CSF is not specific to preeclampsia or eclampsia and forms the adaptive limb of this continuum. Hospitalization itself is the commonest cause of hypomagnesemia. Seizure or convulsion is a life-threatening disorder with possibility of sudden death. Hypomagnesemia allows supraoptimal function of all body function linked to calcium ions in all circumstances, including eclamptic convulsions. Administration of magnesium in ICU in the face of myocardial infarction, pulmonary edema, or pump failure is clearly hazardous. Eclampsia is a self-limited disorder that can resolve spontaneously with delivery and complicates decisive evaluation of potential anti-seizure agents, including magnesium. Magnesium has saved lives and reduced morbidity in preeclampsia / eclampsia as a 'peripheral' anticonvulsant, a unique clinico-pharmacologic situation.

Keywords: preeclampsia; eclampsia; magnesium sulphate; who; blood-brain barrier; hypertension; cerebrospinal fluid; cytokines; tumor necrosis factor-α; albumin-cytological dissociation; pathophysiology; intensive care unit; vasodilator; myocardial infarction; pump failure; chronotropic, inotropic; death; acute kidney injury

Abbreviations:

CA^{++} -- calcium ions

CNS – central nervous system
BBB -- blood-brain barrier
CSF – cerebrospinal fluid

i.v. – intravenous
LMWS – low molecular weight substances
Mg^{++} -- magnesium ions
MRI -- magnetic resonance imaging
s-NMJ –skeletal neuromuscular junction
TNF-α – tumor necrosis factor-alpha
WHO – World Health Organization

Box 1. 10 key learning points:

1. Relative brain hypomagnesemia is not specific to or pathogenetic for eclampsia. Hospitalization itself from any cause is the commonest clinical association of magnesium depletion.
2. Basis of convulsions of eclampsia is presumptive, idiosyncratic, and non-generalizable. Self-limited, variable, and unpredictable nature of eclampsia complicates critical evaluation of seizure-abortive therapy, including magnesium sulfate currently approved by WHO.
3. Homeostatic mechanisms maintain tightly controlled CNS and extra-CNS compartments for magnesium, with large surfeit of Mg++ in cerebral arterial wall and in CSF (200% to 300%, respectively) over systemic arteries. Extracellular Mg reflects 1% of total body content.
4. Exogenously administered oral or i.v. magnesium in high doses does not freely cross the BBB, the clearest evidence of its integrity in preeclampsia / eclampsia. CSF albumin-cytologic dissociation is characteristic of the disorder. Evidence for clinically significant disruption of BBB is absent.
5. Magnesium practically has no specific effect on brain neuronal activity or 'central' / CNS anticonvulsant property or brain-oriented side-effect. Cerebral edema is apparently not linked to eclamptic convulsions.
6. Supraphysiologic doses of magnesium dampen sNMJ function sparing ANS end-plate-junction innervation (pupil, bowel and urinary bladder functions) and brain functions including cranial nerves, cognition and consciousness. Magnesium can induce flaccid quadriparesis and diaphragmatic compromise through sNMJ blockade.
7. Magnesium (Mg++) is a vasodilator, and, acts as a physiological calcium (Ca^{++}) antagonist with low/modest hypotensive action.
8. Magnesium is a diuretic, immediately promoting renal flow and urine formation, and preventing oliguria and acute kidney injury.
9. Magnesium should be used with care in ICU following cardiac and renal compromise. Magnesium induces a double inotropic and chronotropic jeopardy with reduced cardiac output in myocardial infarction complicated with congestive left heart failure, pulmonary edema, and pump failure.
10. Current management of eclampsia with arbitrary WHO-approved regimen of Mg supplementation cannot be supported pharmacologically. Magnesium is a 'peripheral' rather than a 'central' anticonvulsant, in effect a 'pseudo-anticonvulsant'.

Background

Eclampsia remains the major cause of morbidity and mortality (death or near miss) for both the mother and the baby representing one of the principal reasons for admission to intensive care unit (ICU), with a lesser incidence in developed countries that, paradoxically, limits clinical experience with the disease and its complications. [1-5] Eclampsia is characterized by self-limited and unpredictable generalized tonic-clonic seizures not attributable to any other cause. Eclamptic seizure occurs in 2% of women with severe preeclampsia not receiving magnesium sulfate and in <0.6% in those receiving magnesium sulfate. Appropriate surveillance and changes in management protocols, in particular magnesium (Mg) therapy, for prevention of eclampsia in those with severe preeclampsia and acute treatment of eclamptic seizures at all levels of healthcare are required for better maternal and neonatal outcomes. The pathogenesis of eclamptic seizures is not well understood. [1-5] Blood-brain barrier (BBB) enhanced permeability or disruption with passage of fluid, ions, and low molecular weight plasma albumin or dextran into CSF remains the leading theory. Blood-brain barrier permeability may be enhanced by circulating factors found in preeclamptic women, such as vascular endothelial growth factor and placental growth factor. Alteration of autoregulation in the cerebral circulation similar to hypertensive encephalopathy with BBB disruption is also suggested.

The biology of an illness "...is indivisible, has always been holistic in the sense that it considers the whole patient, has always seen the patient balanced between opposing forces pushing her/him towards health or disease as well as considered the ability to continue to function in the face of acute injury or disease process(es) (e.g. preeclampsia / eclampsia), and generates variations in the effects of the same injury/disease in the same individual from time to time just as between individuals". [6,7] "Such a clinical continuum is unlikely to be unifactorial or a 'hopelessly complex' obfuscation, but is probably the result of a meticulously parallel activation of multiple physiologic processes (secondary or adaptive) processes...is not synonymous with 'physiological' 'organic', 'laboratory measurements' or 'nonenvironmental' as has often seemed the case in the medical literature". [6,7] To make meaningful progress in understanding biological nature or pathophysiologic basis of preeclampsia / eclampsia, an overarching, robust, generalizable, and biologically-plausible clinically-valid cause-effect-adaptive continuum needs to be evolved. Besides supportive care and promoting delivery, magnesium sulfate is regarded as an ideal drug for the prevention and treatment of eclampsia, as recommended by the World Health Organization towards achieving the Millennium Development Goals [8].

While the best intravenous (i.v.) therapeutic regimen and the ideal duration of maintenance therapy of Mg are not yet clarified, supraphysiological serum levels between 4 and 7mEq/L do not guarantee that pregnant women with hypertensive disorders are protected against eclampsia. [1-5] In one study, oliguria was the commonest maternal complication recorded with i.v. infusion of magnesium sulfate at 1 gram/hour or 2 grams/hour as a maintenance dose for the prevention of eclampsia. [2] (Discussed below) The basis of adverse neonatal effects seen in women exposed to magnesium sulfate is speculative, and, intriguingly, outcome does not differ in newborn infants at either 1 gram/hour or 2 grams/hour maintenance doses, except for admission to neonatal intensive care, which was more frequent in the 1-gram/hour group (25% vs 6.3%; P=.04). [2] In-depth knowledge of the pharmacokinetics and pharmacodynamics of magnesium sulphate infused i.v. is required for a definitive understanding of the state of dynamic equilibrium between dose administered, its distribution and elimination rate, its efficacy in eclampsia, its side effects in both the mother and the neonate, and to move beyond presumed therapeutic algorithms or clinical suppositions. Such knowledge is missing. [1-5] Only 1% of the total body Mg pool is extracellular, as reviewed. [6,7] Hypomagnesemia in plasma or CSF does not predict eclampsia. To date, there is dearth of data and comprehension regarding Mg transport across BBB, an important caveat for elucidation of pathophysiology of preeclampsia / eclampsia.

Does exogenously administered magnesium in large intravenous doses freely cross the intact or hyperpermeable blood-brain barrier?

The BBB tightly regulates homeostasis of the central nervous system (CNS). Elevated levels of Mg do not freely cross the intact BBB and, conversely, reduce BBB permeability to maintain brain homeostasis in a variety of clinical and experimental circumstances, including acute

hypertension and idiopathic epilepsy. [6,7,9-11] Low levels of serum Mg prevail in acute and chronic neuronal (ischemic stroke, inherited, and neurodegenerative diseases) and extra-neuronal diseases in hospitalized patients as well as in stress and anxiety, as reviewed elsewhere. [6,7,9-11] A protective role of Mg on the BBB itself to reduce its permeability has been presented *in vivo* and *in vitro* model of human BBB possibly related to remodelling of intercellular gap formation, as reviewed recently. [2,6,7] Exogenous i.v. administration of magnesium sulphate in 10 preeclamptic patients maintained mean CSF Mg level in the normal range (3.04 +/- 0.12 mg/dl, range 2.9 to 3.2 mg/dl). [11] In another study of preeclamptic women, CSF ionized, total Mg, and Ca^{++}: Mg^{++}

ratios did not change following magnesium sulphate therapy. [12] Basal levels of free Mg^{++} in CSF are three times that in plasma while the walls of the cerebral arteries have almost double the content of free Mg++ seen in systemic arteries. [13] Such an 'adaptive' or 'protective' distribution of Mg++ is designed to tightly restrict access of exogenously administered Mg into CSF / CNS in order to maintain a critical functional balance between systemic and brain compartments. [6,7] These data indicate that following administration of large pharmacologic doses of Mg in preeclampsia / eclampsia, access of Mg to CSF/CNS is dampened, and that there cannot be any direct relationship between serum and CSF magnesium values. [6,7]

The postulate that exogenously administered Mg does not critically affect brain neuronal function in preeclampsia / eclampsia or in any other brain neuronal disorder cannot be overemphasized and is sustainable both pharmacologically and biologically.

Is blood-brain barrier disruption / hyperpermeability established in eclampsia?

BBB disruption and/or a generalized hyperpermeability has been suggested to prevail in eclampsia by increased CSF concentrations of pro-inflammatory cytokines (IL-6 and IL-8) and TNF-alpha compared to women with normotensive pregnancies (n = 7) and also by elevation of CSF levels of interleukin-6 and TNF-alpha compared to women with preeclampsia (n = 4). [1] Women with preeclampsia also showed increases in pro-inflammatory cytokines but not TNF-alpha in the CSF compared to women with normotensive pregnancies. [1] In particular, women with eclampsia but also women with preeclampsia showed an increase in the CSF to plasma albumin ratio compared to normotensive women. [1] The conclusion that women with preeclampsia and eclampsia show evidence of neuroinflammation and an injured BBB opens a crucial debate.

The human brain is not a passive receptacle to receive pro-inflammatory cytokines and TNF-alpha exclusively from the systemic circulation in diverse circumstances. The brain has its own well-defined auto-immune system independent of the systemic auto-immune or inflammatory or both influences that may have evolved to maximize an organism's ability, anticipatory or contingent, to respond to environmental threats in order to survive without critical disruption of the BBB. Pregnancy is perhaps the best defined teleologic and evolutionarily conserved physiologic organ system that anticipates needs of the mother as well as the neonate. Resident brain cells produce immune system neuromediators such as cytokines, and both systems (nervous and immune) exhibit similar mechanisms of physiologic intercellular communication. [13] Neurons, astrocytes, and microglia produce cytokines and their receptors able to modulate synaptic plasticity, as well as the processes of learning and memory under normal physiologic conditions. [14,15] TNF-α is a critical orchestrator in modulating sensory deprivation-induced homeostatic plasticity in human basal forebrain and mammalian (mouse) olfactory cortex. (16,17) Variable elevations of pro-inflammatory cytokines and TNF-alpha in the CSF can originate from the brain itself under physiologic and stimulated states. Elevation of CSF albumin in preeclampsia / eclampsia results from a non-specific pressure-related movement of a low molecular weight substances (albumin, dextran) following the inextricably linked significant pressure gradient of moderate-to-severe systemic hypertension transferred to small vessels, that, in turn, selectively increases BBB permeability without enhanced diapedesis and can lead to cerebral edema. Rather than a total disruption of BBB integrity, (1) elevation of CSF albumin indicates enhanced hydrostatic pressure driven enhanced permeability. Total disruption of BBB would not sustain the albumin-cytological dissociation typical of preeclampsia / eclampsia. In an unambiguous or total disruption of the BBB, elevation of albumin would be accompanied by presence of red and white blood cells, besides other higher molecular weight substances. The terms BBB injury / impairment [1] must be qualified either as a hyperpermeability or a total non-selective disruption of BBB to reflect truer pathophysiologic status of integrity of BBB. Importance of reversal of such CSF changes following magnesium sulfate therapy [2] will always be questionable since eclampsia is itself a self-limited disorder terminated by delivery, the time frame of which termination is uncertain and variable, i.e., protean. MRI characteristics of brain edema may predict eclamptic seizures in preeclampsia patients with posterior reversible encephalopathy syndrome. [18] Currently, however, cerebral edema does not predict eclamptic convulsion.

In studies of BBB characteristics of preeclampsia / eclampsia, enhanced but selective permeability to low-molecular weight substances and the characteristic albumin-cytological dissociation must be specified. No correlation was also found between plasma angiogenic biomarkers and BBB permeability in preeclampsia. [18] Finally, following mega-dose intravenous Mg supplementation in preeclampsia / eclampsia, CSF magnesium levels do not follow serum magnesium levels correspondingly or at par as might be expected after significant or major pathophysiologic and functional disruption of BBB – probably the most representative, valid, and practical limitation for such theories. There appears to be no major functional or structural injury / disruption of the BBB peculiar or specific to preeclampsia / eclampsia besides the link to rise of hydrostatic pressure due to moderate-to-severe hypertension.

Magnesium and the neuromuscular junction: skeletal and autonomic innervations

Friedman-Korn et al. report reversible postpartum coma-like state following Mg therapy. [20] Besides unimpaired pupillary reflexes in the face of areflexic flaccid quadriparesis and absence of respiratory effort, [20] absence of obtundation or impaired consciousness suggests an extra-CNS prominent skeletal muscle *side-effect* of Mg infusion. Friedman-Korn et al. also report decremental responses on repetitive nerve stimulation in both women. [20] Dysfunction at the skeletal muscle neuromuscular junction (sNMJ), however, is characterized by an initial low-amplitude muscle action potential with progressive decline at low rates of stimulation followed by a progressive increase in amplitudes of successive responses (facilitation) at higher rates of stimulation and after isometric exercise. [21] Concomitant decrease in serum calcium level is important. [21] The variable intensity of sNMJ transmission defect in preeclamptic women receiving standard doses of Mg correlates significantly with increased serum Mg levels, decreased serum Ca levels, and is best correlated with the Mg/Ca ratio. [12,21] The particular predilection for pronounced NMJ dysfunction in some cases with pre-eclampsia admitted to ICU may involve markedly lowered plasma cholinesterase levels, subclinical thyroid dysfunction, and clinically-covert auto-immune disease. [21-23] Autonomic neuromuscular transmission, involving ATP, noradrenaline, or acetylcholine, is not involved by Mg. [24,25]. Besides pupillary reflexes, all ANS functions, including bowel and urinary bladder functions, remain unaffected by large doses of Mg. Magnesium oxide is an established laxative. [26] Magnesium decreases post-operative urinary retention. [27]. Anti-epileptic effect of large i.v. doses of Mg in preeclamsia / eclampsia

probably involves a major generalized dampening effect on the sNMJ rather than a primary brain neuronal stabilizing influence.

Generalized vasodilator effect of magnesium in ICU

The primary Ca^{++} antagonist vasodilator function of Mg is not generally appreciated. [6,7,10,27,28] Magnesium administration increases cardiac output and minimises hypotension in patients without cardiovascular complications. The chronotropic and inotropic jeopardy of Mg supplementation manifests only in severe myocardial infarction with pump failure (left heart failure or cardiogenic shock or both) and deaths in ICU. [10,28,29] Oliguria following i.v. Mg supplementation for eclampsia [2] is another warning parameter in ICU indicative of diminished renal perfusion. Vasodilators, in general, do not decrease urine output. Oliguria is an established feature of severe preeclampsia. [1-5] Administration of 1-3g i.v. Mg before cisplatin is suggested as the best practice regardless of baseline serum Mg level to immediately increase urine output and to prevent cisplatin-induced acute kidney injury without reducing its chemotherapeutic efficacy. [30] Use of Mg in the ICU in general, and in eclampsia, therefore, must be guarded.

Conclusion

Currently, magnesium sulfate is the anticonvulsant of choice to treat or prevent eclampsia when indicated. WHO-recommended role of magnesium therapy in management of eclampsia, however, needs reconsideration. Exogenously administered magnesium does not freely cross the intact blood-brain barrier. A characteristic albumin-cytological dissociation is maintained in CSF in preeclampsia / eclampsia. Blood-brain barrier remains largely intact in preeclampsia / eclampsia with hydrostatic hyperpermeability to low molecular weight substances, including albumin and dextran. Failure of CSF magnesium levels to correspondingly rise following massive i.v. doses of magnesium are the clearest indication of maintenance of two homeostatic compartments of magnesium by the human body as well as of the functional integrity of the blood-brain barrier. Cytokines and tumor necrosis factor-α form part of the natural repertoire of the human / mammalian brain to develop and maintain plasticity. Anticipatory and contingent adaptation of the human brain to stress of moderate-to-severe hypertension of preeclampsia / eclampsia is crucial to evolutionary survival. Low / relatively low magnesium levels in serum and CSF despite large dose presumedly therapeutic infusion of magnesium sulfate form part of the cause-effective-adaptive continuum that maintains integrity of the organism in the face of life-threatening convulsions of eclampsia.

Expert Opinion

The BBB is the key structure that maintains a distinct compartment for magnesium at the level of the brain, to allow for a guarded milieu interior enabling optimal function of CNS neurons. The role of magnesium itself is critical in maintaining homeostasis at the level of the CNS. The development of systemic hypomagnesemia has to be viewed critically in clinical medicine, particularly in moderate-to-severe hypertension and with cardiac compromise. Act of hospitalization is the commonest etiology of hypomagnesemia in the systemic circulation. Magnesium content of cerebral arterial wall and CSF and is 200% to 300% that of systemic arterial wall, respectively. Transfer of magnesium across the BBB is carefully regulated to allow for adaptive CNS neuronal function under a wide spectrum of clinical circumstances. As the physiological antagonist of calcium ions (Ca^{++}), magnesium ions (Mg^{++}) importantly regulate BBB permeability and dampen transfer of Mg^{++} across the BBB. Following WHO-recommended regimen of massive infusion of magnesium sulfate for managing preeclampsia / eclampsia, CSF magnesium levels do not rise in parallel but remain within the normal range, a characteristic-to-pathognomonic neurotherapeutic laboratory feature. Hyperpermeability of BBB in preeclampsia with selective passage of low-molecular weight substances (LMWS) such as interleukins, tumor necrosis factor-α, albumin, and dextran is not tantamount to a total physico-chemical disruption of the BBB. Passage of LMWS into the CNS in preeclampsia / eclampsia possible involves a hydrostatic-pressure related transfer across the BBB. In addition, the brain has its own auto-immune system to manage synaptic plasticity, learning, and memory under normal physiologic conditions. A characteristic albumin-cytological dissociation prevails in preeclampsia / eclampsia. The WHO-guideline for role of magnesium therapy in management of self-limited convulsions of eclampsia is arbitrary and debatable. Magnesium does not have any intrinsic or generalized anti-convulsant activity. In supraphysiologic doses, magnesium depresses sNMJ function while sparing autonomic functions and brain functions, including cranial nerves, cognition, and consciousness, a unique and pathognomonic 'pseudo-anticonvulsant' action. Large pharmacologic doses of magnesium do not guarantee management of convulsions of eclampsia. As the distinction between 'hyperpermeability' versus 'disruption' of BBB in preeclampsia / eclampsia evolves, along with the concept of distinct 'systemic or extra-CNS' and 'CNS' compartments for magnesium in human neurophysiology, use of magnesium as an anticonvulsant in preeclampsia / eclampsia will be further rationalized. In the next five-years, I envisage that the physiology of magnesium at the level of CNS / CSF and / or the skeletal NMJ will be better understood.

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