MAGNESIUM SULPHATE IN THE MANAGEMENT OF ECLAMPSIA

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- Eclampsia, the occurrence of a convulsion (fit) in association with the syndrome of pre-eclampsia, is a rare but very serious complication of pregnancy.

- Pre-eclampsia is a multisystem disorder that is associated with raised blood pressure (>140/90) and proteinuria beyond 20 weeks of pregnancy.

- About one-third of women will have their first fit after delivery of the baby (Knight 2007).

- Estimated to complicate around 1 in 2000 deliveries in Europe and other high-income countries (Douglas 1997), and from 1 in 100 to 1700 deliveries in low- and middle-income countries (Crowther 1985).

- Eclampsia is associated with around 10% of maternal deaths and an estimated 50,000 women die each year having had an Eclamptic convulsion (Duley 1992:Khan 2006)

- Magnesium Sulphate was one of the earliest agents suggested to have a specific anticonvulsant action in treatment of eclampsia.

- The first published account of this suggestion appeared in 1906 (Horn, from Chesley 1978) .

- By the late 1920s, magnesium sulphate was being used for the treatment of women with eclampsia in both Europe and US (Dorsett 1926 ; Lazard1925).

- Over the subsequent years, a range of alternative drugs have also been advocated for eclampsia.

- Diazepam (Lean 1968), for example, being cheap and readily available, rapidly became popular in both developed and developing countries.

- In the 1980s, Phenytoin was proposed (Slater 1987) as having the theoretical advantage of controlling convulsions whilst avoiding sedation.

- For decades, controversy raged as to which agent was preferable for women with eclampsia (Dinsdale 1988;Donaldson 1992;Kaplan 1988;Sibai 1990).

- This controversy was concluded when a large randomized trial demonstrated that magnesium sulphate was preferable to either diazepam or Phenytoin (Collab Trial 1995).

- Cochrane reviews confirm that **Magnesium sulphate is better** than diazepam, Phenytoin or Lytic cocktail (usually a mixture of chlorpromazine, Promethazine and Pethidine) for treatment of women with eclampsia (Duley 2000).

COCHRANE DATABASE SYST REV. 2003;(2):CD000025.

- **Magnesium sulphate and other anticonvulsants for women with pre-eclampsia.**
  Duley , Henderson-Smart D J,Gulmezoglu A M

- OBJECTIVES: The objective was to assess the effects of anticonvulsants for pre-eclampsia on the women and their children.

- CONCLUSIONS: Magnesium sulphate more than halves the risk of eclampsia, and probably reduces the risk of maternal death. A quarter of women have side effects, particularly flushing.

COCHRANE DATABASE SYSTEM REV. 2003;(4):CD000127-128.

- **Magnesium sulphate versus diazepam for eclampsia.**

  Duley L , Henderson-Smart D J

- OBJECTIVES: The objective of this review was to assess the effects of Magnesium sulphate compared with diazepam when used for the care of women with eclampsia.

- CONCLUSIONS: Magnesium sulphate appears to be substantially **more effective than diazepam** for treatment of eclampsia.

COCHRANE DATABASE SYSTEM REV. 2001;(1):CD002960.

- **Magnesium sulphate versus lytic cocktail for eclampsia.**

  Duley L ,Gulmezoglu A M

- OBJECTIVES: The aim of this review was to compare the effects of magnesium sulphate with those of lytic cocktail when used for the care of women with eclampsia.

- CONCLUSIONS: Magnesium sulphate is the anticonvulsant of choice for women with eclampsia.
  Lytic cocktail should be abandoned.

COCHRANE DATABASE SYST REV. 2003;(4):CD000128.

- **Magnesium sulphate versus phenytoin for eclampsia.**

  Duley L ,Henderson Smart D

- OBJECTIVES: The objective of this review was to assess the effects of Magnesium sulphate compared with Phenytoin when used for the care of women with eclampsia.

- CONCLUSIONS: Magnesium sulphate is substantially more effective than Phenytoin for women with eclampsia.

MODE OF ACTION FOR MAGNESIUM SULPHATE

Exactly how magnesium sulphate might control

Eclamptic convulsions is unclear.

VASCULAR EFFECTS OF MAGNESIUM SULFATE.

- Magnesium is a potent vasodilator of uterine and mesenteric arteries, and aorta, but has minimal effect on cerebral arteries.
- In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC).
- Decreased calcium channel activity lowers intracellular calcium, causing relaxation and vasodilation.
- Magnesium also increases NO production causing vasodilation.

- **Belfort MA, Moise KJ Jr.** Effect of magnesium sulfate on maternal brain blood flow in preeclampsia: A randomized, placebo-controlled study. ***Am J Obstet Gynecol*. 1992; 167: 661-666.**
- **Naidu S, Payne AJ, Moodley J, Hoffmann M, Gouws E.** Randomised study assessing the effect of phenytoin and magnesium sulphate on maternal cerebral circulation in eclampsia using transcranial doppler ultrasound. ***Br J Obstet Gynaecol*. 1996; 103: 111-116**

EFFECT ON CEREBRAL EDEMA AND THE BLOOD-BRAIN BARRIER.

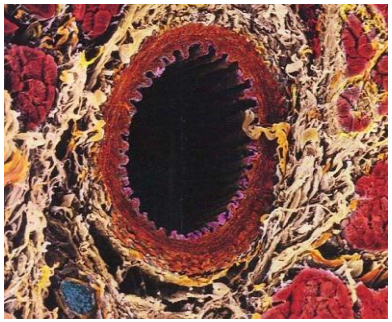
- The calcium antagonistic effects of Magnesium can also affect the cerebral endothelium that forms the blood-brain barrier.
- Decreased cell calcium inhibits endothelial contraction and opening of tight junctions that are linked to the actin cytoskeleton.
- Decreased tight junction permeability limits paracellular transport of vascular contents, ions, and proteins that can promote vasogenic edema and seizures.
- It is also possible that magnesium sulfate diminishes transcellular transport by limiting pinocytosis, which is known to occur rapidly during acute hypertension.

- **Turkoglu OF, Eroglu H, Okutan O, Tun MK, Bodur E, Sargon MF, Öner L, Beskonakli E.** A comparative study of treatment for brain edema: Magnesium sulphate versus dexamethasone sodium phosphate. ***J Clin Neurosci*. 2008; 15: 60-65**

ANTICONVULSANT ACTIVITY OF MAGNESIUM SULFATE.

- It has its role as a blocker of N-methyl-D-aspartate (NMDA) receptors in the brain.
- Seizures consist of an excessive release of excitotoxic neurotransmitters including glutamate.
- Excessive glutamate can activate the NMDA receptor, leading to massive depolarization of neuronal networks and bursts of action potentials.
- Magnesium may act to increase the seizure threshold by inhibiting NMDA receptors, thereby limiting the effect of glutamate.

- **Goldman RS, Finkbeiner SM.** Therapeutic use of magnesium sulfate in selected cases of cerebral ischemia and seizure. ***N Engl J Med*. 1988; 319: 1224-1225.**
- **Hallak M, Berman RF, Irtenkauf SM, Janusz C, Cotton DB.** Magnesium sulfate treatment decreases N-methyl-D-aspartate receptor binding in the rat brain: An autoradiographic study. ***J Soc Gynecol Invest*. 1994; 1: 25-30.**
- **Lipton SA, Rosenberg PA.** Excitatory amino acids as a final common pathway for neurologic disorders. ***N Engl J Med*. 1994; 330: 613-620.**

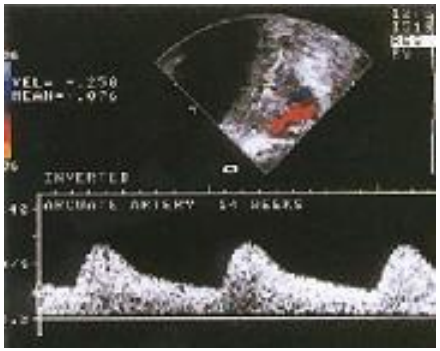


Mechanism : $Mgso_4$

Protect Endothelial Cells

PGI_2, NO ↑

Cerebral Perfusion ↑



Naidu S, Payne AJ, Moodley J, Hoffmann M, Gouws E. Randomised study assessing the effect of phenytoin and magnesium sulphate on maternal cerebral circulation in eclampsia using transcranial doppler ultrasound. *Br J Obstet Gynaecol*. 1996; 103: 111–116

MODE OF ACTION FOR MAGNESIUM SULPHATE : SUMMARY

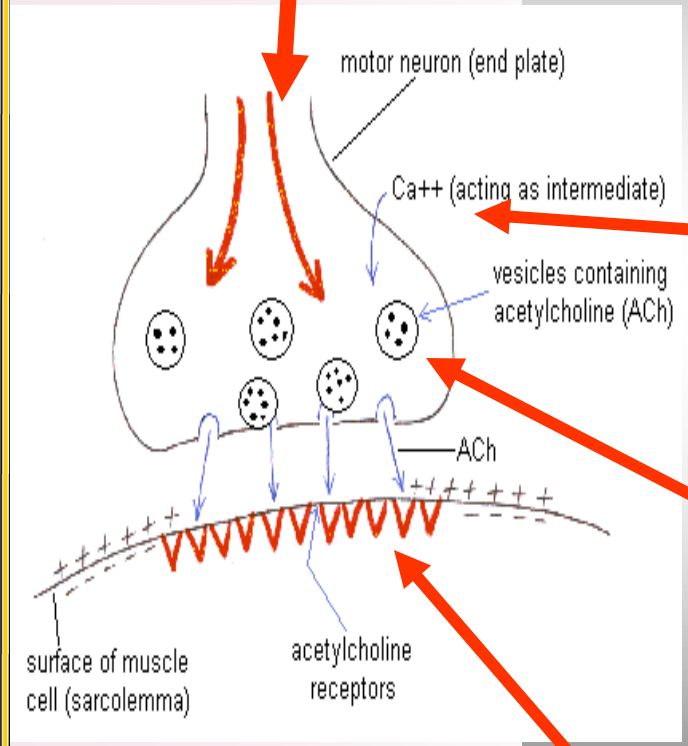
- **Stroke.2009;40:1169-1175**

- **Magnesium Sulfate for the Treatment of Eclampsia**
- **Anna G. Euser, PhD Marilyn J. Cipolla, PhD**

- Though the specific mechanisms of action remain unclear, the effect of Magnesium sulfate in the prevention of eclampsia is likely multi-factorial.
- Magnesium sulfate may act as a vasodilator, with actions in the peripheral vasculature or the cerebro-vasculature, to decrease peripheral vascular resistance or relieve vasoconstriction.
- Additionally, magnesium sulfate may also protect the blood-brain barrier and limit cerebral edema formation.
- And it may act through a central anticonvulsant action.

Mechanism : $Mgso_4$

Neuromuscular Conduction slowed → Neuronal Burst Firing → Abort Convulsion



N-Methyl D-Aspartate Receptors Blocked → Ca^{++} entry blocked → Abort Convulsion

Ach secretion by motor nerve end ↓ → Prevent Convulsion

Sensitivity of end plate to Ach ↓ → Prevent Convulsion

ADVERSE EFFECTS …

The most reliable data to date on side effects and potential hazards of Magnesium sulphate, compared to placebo, come from **Magpie Trial (2002)** which recruited over 10,000 women.

- The most common side effect is **flushing.**
- Others include- nausea, vomiting, muscle weakness, thirst, headache, drowsiness and confusion.
- Magnesium sulphate can lead to respiratory depression and respiratory arrest, these hazards appear to be rare and with unmonitored high doses.

- Decreased uterine activity and prolonged labor , slow cx dilatn.
- Decreased fetal heart rate variability.
- Blood loss after delivery—Slightly more.
- Neonatal neuromuscular and respiratory depression.
- Low Apgar scores
- Decreased vital capacity.
- Risk of pulmonary edema.

PREPARING DOSAGES OF MAGNESIUM SULPHATE

- It is available as 50% w/v and 25% w/v ampoules.
- **50%w/v , 2 ml ampoule = 1 gram $MgSO_4$ - used for both I.M. as well as I.V.**
- **25% w/v 2 ml ampoule = 0.5 gram $MgSO_4$ – used for only I.V. route.**

INTRAVENOUS MAGNESIUM SULPHATE

- 4 ampoules of 50% solution = 4 gm (8 ml)
- It is diluted in distilled water (12ml) to make it 20 ml and give it slow IV.
- At least 5 minutes should be taken to inject 4 gm.
- If **25 %** solution is used then **8** ampoules have to be taken(16 ml); dilute till 20 ml.

INTRAMUSCULAR MAGNESIUM SULPHATE

- 5 ampoules of 50% solution = 5 gm (10 ml)
- Should be given as deep IM injection in the buttocks.
- Add 1 % Xylocaine 1 ml to minimize the pain at site.

- 25% soln not to use as vol will be 20 ml.

I.V. / I.M.

- There was **no evidence** from the Collaborative Trial **of any difference** between the intramuscular and intravenous regimens in their effects on recurrent convulsions.
- However intramuscular injections are painful and are complicated by local abscess formation in 0.5% of cases.

- When magnesium sulfate is admin **IV**, the **onset** of action is **immediate** and the duration of action is about 30 min.
- Following **IM** admin of the drug, the onset of action occurs in about 1 hr and the **duration** of action is **3-4 hr**.
- Onset – IV < IM
- Duration Of Action – IV < IM

Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995; 345:1455.1463

[McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2002. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2002 (Plus Supplements)., p. 2164]

MONITORING ----

- **The maintenance dose of Magnesium Sulphate is given only after assuring that:**

- Patellar reflex is present
- Respiration not depressed. (RR > 16/min)
- Urine output during previous 4 h- exceeded 100 mL. (25ml/hr)

- **Serum monitoring of Magnesium levels has been advocated, but is expensive and has not been shown to be superior to clinical monitoring.**

ALTERNATIVE REGIMENS FOR MAGNESIUM SULPHATE

- **Lazard 1925– A first ever report**
- Very low dose of 2-4 g was administered I.V.

  Disadvantage.- **Poor control** due to not achieving required plasma conc. of $MgSO_4$.

- **Eastman 1945** - suggested that women be given 10 g as an intramuscular injection followed by 5 g every six hours.

  Disadvt.- Plasma concentrations rise slowly after intramuscular injection so **in status eclampticus it was not effective.**

ACCEPTED WORLDWIDE

- **Pritchard 1955** –

  Suggested changing the loading dose to 4 g by intravenous infusion as 20% soln at a rate not to exceed 1g/min, and increasing the maintenance dose to 5 gm I.M. every 4 hour.

  This regime is still widely used, particularly in the developing world.

- Disadvantage. - Pain and infection at the I.M. injection site.

- **Zuspan 1978 -**

  Loading dose is 4 g I.V. infusion as 20% solusion

  at a rate not to exceed 1g/min,

  followed by an infusion of 1 g per hour.

  This is the standard intravenous regime, widely used in many countries.

- **Sibai 1984,1990 –**

  Loading dose is 6 g in 100 ml of I.V fluid to be administered

  over 15-20 min.

  Maintenance dose – 2g /hour in 100 ml as slow infusion.

EVIDENCE …

- **The regimens suggested by Pritchard and Zuspan are the two that have been evaluated in the randomized trials of anticonvulsants for women with eclampsia and pre-eclampsia (Duley 1996).**

- In most of these trials, clinical monitoring was used: hourly measurement of urine output, with regular checking of the respiration rate and tendon reflexes.

- **Serum monitoring of magnesium levels has been advocated, but is expensive and has not been shown to be superior to clinical monitoring.**

OTHER LOW DOSE REGIMENS:

- **Dhaka Regime -** The loading dose of magnesium sulphate was 10 gm.
  Following this 2.5 gm was given intramuscularly 4 hourly,
  for 24 hours after administration of the first dose.
- Disadvt. – Small sample size of trial; More randomized trials are required.

- **Dr.Sardesai ,Solapur -** loading dose of magnesium sulphate 4 gm i.m. or I.V.
  in 20 cc 25 % dextrose .
  Following this 2 gm I.M / diluted I.V , 3 hourly.

More sustained levels of Mg ++ are achieved , with better control and low dose.

This regime is well followed in rural and interior southern Maharashtra with good outcome.

OTHER LOW DOSE REGIMENS:

- **PADHAR REGIME :** 6 - 10 g loading dose of magnesium sulphate.
  4 g maintenance dose every 4 h.

- Advt - It demonstrated that if patient has received dizepma/pheneragan before referral , loading dose can be reduced.

- Disadvt. – Small sample size of trial; More randomized trials are required.

MANAGEMENT OF TOXICITY –

RARE OCCASION IF MONITORED PROPERLY OR WITH RENAL UPSET

- Prompt tracheal intubation
- Mechanical ventilation

} In case of resp. depression.

- 10% Calcium Gluconate 10 ml slow I.V over 10 min with cardiac monitoring and then as and when required.
- Stop further Magnesium Sulphate doses.

GUIDELINES FOR MANAGEMENT OF POTENTIAL COMPLICATIONS OF MAGNESIUM SULPHATE

1. ***Respiratory arrest***
   •To stop magnesium therapy. •To give 1 gm calcium gluconate I/V -The antidote for magnesium toxicity •To intubate and ventilate immediately.•Ventilation should be continued until the resumption of normal spontaneous respiration.

2. ***Respiratory depression***
   •To stop magnesium therapy •To give 1 gm calcium gluconate I/V •To give oxygen by mask •To maintain airway and •To nurse in the recovery position ,

3. ***Absent patellar reflexes***
If respiration is normal, further doses of $MgSO_4$ to be withheld until the reflexes return, if respiration is depressed then management to be as in 2 above. $MgSO_4$ can be restarted if considered necessary once reflexes have returned but at a reduced dose unless there have been further convulsions.

4. ***Urine output-< 100 ml in 4 h.***
If there are no other signs of magnesium toxicity, the next I/M dose of $MgSO_4$ to be reduced to 2.5 gm or the I/V infusion to 0.5 gm/h . Particular attention to be paid to fluid balance and blood loss.

- ***Eclampsia Trial Collaborative Group.*** *Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial.* ***Lancet 1995;*** *345:1455.1463.*

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THANK YOU !

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