The MAGPIE-Trial [The MAGPIE Trial Collaborative Group 2002] (MAGnesium for PreventIon of Eclampsia)

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Abstract

In 10 141 women with pre-eclampsia (RR ≥ 140/90 mmHg, proteinuria) the randomised, double blinded, placebo-controlled, multicenter and confirmatory study showed that magnesium sulphate significantly reduce the risk of eclampsia over 50% and lead not to a significant higher mortality and morbidity of the children. MAGPIE showed partially an improvement of the maternal morbidity and is not excluded t hat the maternal mortality can be reduced by magnesium sulphate.

Introduction

Pre-eclampsia is a multisystem disorder of pregnancy usually associated with raised blood pressure between the 20. week of gestation and the end of the 1. week after birth and proteinuria, which complicates 2 – 8% of pregnancies. The disease can also lead to a weight gain of 1 – 2kg per week and prodromal symptoms like blurred vision, frontal headache, double seeing, nausea and epigastric tenderness.

Pre-eclampsia seems to increase with age, especially with a familiar history, but also in some ethnies like indians, black women and inhabitans of the fidschi-islands, with hyperplacentosis, stress and primiparous.

Because of cerebral haemorrhage, convulsions (eclampsia), cortex blindness, ablatio of the retina, HELLP-syndrome (haemolysis, elevated liver enzyms, and thrombozytopenia), liver rupture, disseminated intravasale coagulation, edema of the lungs and larynx, renal damage, placenta abruption, and asphyxia of the fetus pre-eclampsia is a danger for the mother and the child.

The therapy of pre-eclampsia is composed of bedrest, supervision of the patient, diet and drugs like benzodiazepines, phenytoin, lytic cocktail, low dose aspirin and magnesium sulphate. The therapy with low dose aspirin could not be proved [Wallenburg 2002] and magnesium sulphate showed to be superior to diazepam and phenytoin [Eclampsia Trial Collaborative Group 1995, Lucas et al 1995].

To recommend magnesium sulphate worldwide for the therapy of pre-eclampsia to reduce the risk of eclampsia and to get reliable information for the risks of the child and the outcome for the women the large MAGPIE Trial was initiated.

Study design

Women were eligible for trial entry if they had pre-eclampsia and there was uncertainty about wether to use magnsium sulphate. The women were included irrespective of wether they had had an anticonvulsant before. Women could be recruited who had not given birth, or was 24 hours or less post partum. The definition of pre-eclampsia was blood pressure 90 mmHg diastolic or 140 mmHg systolic or more on at least two occasions, and proteinuria 1+ (30mg/dl).

The exclusion or non-inclusion criteria were hypersensitivity to magnesium, hepatic coma with a risk of renal failure, or myasthenia gravis. Women with oliguria (urine output < 25 ml/h) were eligible, but the volume of trial treatment was halved for each dose.

Women were randomly allocated to receive either magnesium sulphate or placebo. The loading dose was 4g magnesium sulphate, or placebo, given intravenous over 10 – 15 min. The maintenance regimen could be an intravenous (iv) ot intramuscular (im) route. The i v maintenance regimen was an infusion of 1g/h over 24h, and for the i m regimen the initial i v dose was combined with i m injection of 5g into each buttock and followed every 4h for 24h. In the patients with oliguria the dosis were to be halved. The tendon reflexes and respiratory rate were to be regularly controlled.

Randomisation was done by a central telephone, using a minimisation algorithm for severity of pre-eclampsia, gestation at randomisation, wether delivered, given anticonvulsant drugs before, multiple pregnancy, country, and in 8 treatment blocks.

Primary outcomes were eclampsia and, for women randomised before delivery, death of the baby. Secondary outcomes were maternal mortality and morbidity and morbidity of the child.

Subgroups were a priori classified. (e.g. severity of pre-eclampsia, imminent eclampsia, gestational age, anticonvulsants, and countries of different perinatal mortality).

The simple size estimation started with the risk of convulsions be about 1%, but revisited with 1.2%. Between 10 800 and 12 750 women would be necessary to show a 50% decrease of the risk of convulsions with α=0,05 and a power of 90%. If total mortality for the babies was reduced from 10% tp 8.5% (15% reduction) the power would be 80% (α=0.05) with this sample size estimation. One of the primary outcomes should reach a p value of about 0.003.

After the review of data for 8 483 women the trial was stopped.

Results

Of the 10 141 women 8 804 were randomised before and 1 337 after labour. 5 055 women in each group could be analysed. 47% were recruited in Africa, 27% in the Americas, 15% in the Asia-Pacific region, and 10% in Europe. The rate not received allocated treatment was low (about 3%). The groups were well balanced at trial entry. The compliance was high (>90%). The i v route for maintenance therapy was used in 25 countries, the i m route in 15 countries. 16% in the magnesium sulphate group and 12% in the placebo group stopped treatment early.

Eclamptic convulsions were significantly fewer in the magnesium sulphate group with 0.79% than in the placebo group with 1.90%. The relative risk reduction amounted to 58% and the absolute risk reduction to 1.11%.

The number needed to treat to prevent one eclampsia is 91 women.

The difference is significant with a p value of <0.001 and the power of this results is over 90%.

The risk reduction was independet from the severity of pre-eclampsia, but especially if the randomisation were done after the 34. week before delibery, there was an imminent eclampsia, no anticonvulsants were given before trial, and the women were recruited in a country with a high perinatal mortality rate (> 40 deaths per 1000 births).

12.7% of the babies died in the magnesium sulphat and 12.4% in the placebo group. The higher relative and absolute risk of 2.0% respectively 0.3% is not significant.

The maternal mortality could be reduced relatively by 45% and absolutely by 0.18%. The difference was not significant. The most frequent cause of death was eclampsia. For the outcomes of maternal morbidity there was a significant reduction in placental abruption by magnesium sulphate.

Deficiencies of the trial

Women living under very different circumstances were recruited in the trial.

The were a different maintenance therapy with the treatment.

The concomitant therapy was not standardized.

There was no measurement of the serum content of magnesium.

The randomisation was achived by the minimisation method.

There was no follow-up study of the patients not recruited in the trial.

The incidence of eclampsie was with 1.9% distinctly lower than assumed with 1.0% respectively 1.2%

Valuation of the study

MAGPIE is a confirmatory study with an estimated incidence of convulsions in the patients with pre-eclampsia of 1.2% and a relative risk reduction by magnesium sulphat versus placebo of 50%, resulting in a sample size estimation between 10 800 and 12 750 women.
In spite of the stop of the trial the minimal number of patients with 10 141 was nearly reached. The relative risk reduction of 50% was surpassed with 58%. The power was over 90% and the result can be considered as proved.
The value of one of the primary outcomes of 0.003 was excelled with < 0.001. The higher incidence of convulsions with 1.9% instead of 1.2% assumed favoured the result.
The deficiencies like different circumstances in the countries, different maintenance therapy for the trial treatment, no standardising of the concoment therapy are distributed nearly equal in both groups and it is not to exspect that the structure of the group will be disturbed.

"Blood monitoring of magnesium concentrations was not required" [The MAGPIE Trial Collaborative Group 2002], however Kisters et al. [1990] found in 27 patients with pre-eclampsia and in 22 healthy pregnant women, that the plasma Mg^{2+} concentrations was not significantly different in the pre-eclamptic and the healthy pregnant women, but the values were significantly lower compared with the normal range. The intraerythrocytic Mg^{2+} concentration was significantly lower in the pre-eclamptic patients and in the healthy pregnant women compared with the normal range, but the values were significantly lower in the pre-eclamptic patients than in the healthy pregnant women. After treatment with Mg^{2+} salts there was a normalization of the plasma Mg^{2+} concentrations, but not the intraerythrocytic Mg^{2+} concentration.

Compared with non-pregnant subjects Kisters et al. [1998] found significantly lower plasma Mg^{2+} concentration in pre-eclamptic patients and healthy pregnant women. The intraerythrocytic Mg^{2+} concentration was significantly lower in pre-eclamptic patients compared with healthy pregnant women. After Mg^{2+} supplementation in the pre-eclamptic group, plasma Mg^{2+} concentration normalized, but intracellular Mg^{2+} deficiency could not be corrected completely. In eryrthrocyte membranes, the Mg^{2+} content was found significantly decreased in the pre-eclamptic women as compared to healthy pregnant and nonpregnant subjects.

In a further study Kisters et al. [2000] confirmed that in pre-eclamptic patients and healthy pregnant women the plasma and intracellular Mg^{2+} concentration is significantly lower compared

with controls. In erythrocyte membranes magnesium content was found significantly decreased in the pre-eclamptic women as compared to healthy subjects. There was a signifcant decrease in the plasma calcium concentration in the pre-eclamptic group compared to controls or healthy pregnant women, but membranous calcium content was significantly increased in the pre-eclamptic group versus controls or healthy pregnant women.

Kisters et al.[1990, 1998, 2000] conclude from their results that lowered intracellular plasma and membrane magnesium concentrations in pre-eclampsia may contribute to the development of hypertension in pregnancy and in addition, a disturbed calcium homeostasis is obseved in pre-eclampsia.

The importance of the minimisation method of randomisation will be discussed but used in large studies like ISIS-4 [ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group 1995].

Conclusions

MAGPIE proved that in patients with pre-eclampsie eclampsie can be reduced by magnesium sulphat.

The mortality and morbidity of the children will not be increased by the therapy with magnesium sulphate.

Because of the very low incidence it is not excluded that by magnesium sulphate the maternal mortality can be reduced.

The maternal morbidity can partly be improved by magnesium sulphate.