Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial

Simon J, Gray A, Duley L, Magpie Trial Collaborative Group

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The present study compared the use of magnesium sulphate (MgSO4) in women with pre-eclampsia with no such prophylaxis (placebo), within the context of the Magnesium Sulphate for Prevention of Eclampsia (Magpie) Trial. Clinical monitoring of urine output, respiratory rate and tendon reflexes was used for both regimens. All other aspects of care were according to local clinical practice. Further details were given in the parent study (The Magpie Trial Collaborative Group 2002, see 'Other Publications of Related Interest' below for bibliographic details). The treatment regimen was an intravenous bolus followed by 24-hour maintenance therapy, the route of which was chosen by each centre.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Women with pre-eclampsia were eligible for trial entry if there was uncertainty about whether to use MgSO4 and they had not given birth or were within 24 hours of delivery. The population for the Magpie Trial were described elsewhere (The Magpie Trial Collaborative Group, 2002).

Setting
The setting was secondary care. The economic evaluation was carried out in 33 countries.

Dates to which data relate
The effectiveness evidence and resource use data were collected between 1998 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken retrospectively on the same patient sample as that used in the parent effectiveness study.

Study sample
In the parent study, 10,141 women were randomised from 33 countries. Follow-up data were available for 10,110 women. Finally, data from 9,996 pregnancies were included in the present economic evaluation: 1,195 from high gross
national income (GNI) countries, 5,571 from middle GNI countries and 3,230 from low GNI countries. Of the 10,110 women in the clinical analysis, 114 (1%) were excluded because resource use data were missing or incomplete, either for the babies (n=105) or the women (n=9). Power calculations were not reported.

**Study design**
This was a randomised placebo-controlled study that was conducted in 33 countries. The patients were followed up until discharge from hospital after delivery, or until death. The method of blinding and any losses to follow-up were not reported in the current study. The methods used in the parent study were described elsewhere (The Magpie Trial Collaborative Group, 2002).

**Analysis of effectiveness**
It was not reported whether the analysis was conducted on the basis of intention to treat or on treatment completers only. The primary health outcomes used in the analysis were eclampsia, maternal death and, for women randomised before delivery, death of the baby (including stillbirths). The relative risk (RR) of eclampsia was also reported according to national income. It was not reported whether the two patient groups were comparable in terms of their baseline characteristics.

**Effectiveness results**
The main outcomes for women and babies included in the economic evaluation were as follows:

- Maternal death was 0.2% in the MgSO4 group versus 0.4% in the control group.
- Eclampsia was 0.8% in the MgSO4 group versus 1.9% in the control group.
- Total baby death was, for babies whose mother was randomised before delivery, 13% in the MgSO4 group versus 12% in the control group.
- Stillbirth was 8% in the MgSO4 group versus 9% in the control group.

The RR of eclampsia with MgSO4 was 0.42 (95% confidence interval, CI: 0.29 to 0.61). The RR was 0.60 (95% CI: 0.14 to 2.50) for the high GNI group, 0.64 (95% CI: 0.39 to 1.04) for the middle GNI group, and 0.23 (95% CI: 0.12 to 0.43) for the low GNI group.

**Clinical conclusions**
The parent study (The Magpie Trial Collaborative Group, 2002) provided robust evidence that MgSO4 more than halved the RR of eclampsia, and this was further supported by other relevant trials. As the baseline incidence of eclampsia was higher in low income countries than in higher income ones, the absolute risk reduction associated with MgSO4 varied substantially across the three GNI groups.

**Measure of benefits used in the economic analysis**
The number of cases of eclampsia prevented was chosen as the measure of benefit for the present analysis. To estimate the number of cases of eclampsia prevented in each group of countries, the RR of eclampsia was calculated within that group. This RR was then applied to the baseline risk of eclampsia to obtain an average absolute risk reduction. Discounting of the outcomes was not necessary given the relatively short time period of the analysis.

**Direct costs**
The total cost per pregnancy, including both woman and baby, was calculated as the sum of the treatment cost and other costs. The treatment costs covered MgSO4 and its administration (i.e. staffing, equipment and consumables). Treatment administration was valued according to country-specific clinical practice. The "other costs" category covered all other costs.
aspects of hospital care in the trial, such as treating pre-eclampsia, eclampsia or the side effects of MgSO4 treatment. It included the costs of antenatal and postnatal ward stay, high dependency and/or intensive care, artificial ventilation, delivery and medication for the mother, as well as the costs of hospital stay, neonatal intensive care and artificial ventilation for the baby if the mother was randomised before delivery. Resource items that were evenly balanced between the trial arms and were used for less than 5% of pregnancies (e.g. renal dialysis, transfusion, cerebral imaging) were not included. Hospital resource use data were available for the trial period from the Magpie Trial. Country-specific unit costs were obtained subsequently from participating hospitals by means of a questionnaire. The follow-up time frame for the economic evaluation was from randomisation until 6 weeks, discharge from hospital after delivery, or death, whichever occurred earlier.

All unit costs were adjusted using national consumer price indexes, and then converted into US dollars using exchange rates. Missing unit cost and clinical practice data were imputed using values from the most similar country in terms of economic status and geographical area, supplemented with information from the International Drug Price Indicator Guide. Discounting of the costs was not necessary given the relatively short time period of the analysis. The price year was 2001.

**Statistical analysis of costs**

The costs were treated stochastically. To control for the influence of the many factors not related to the trial over the "other costs" category, the influence of eclampsia on that variable was estimated using multivariate regression analysis in each group. National income and eclampsia were used as predictive factors. Patient-specific other costs were then estimated by entering each woman's observed values of the predictive factors into the regression equation. The cost-effectiveness results were calculated using this regression-adjusted "other costs" data. Non-parametric bootstrapping was used to calculate the 95% CI for the three incremental cost-effectiveness ratio (ICER) point estimates. A cost-effectiveness acceptability curve for each GNI group was also reported, to show the probability that prophylactic MgSO4 was cost-effective at different values of the decision-makers' willingness-to-pay to prevent a case of eclampsia.

**Indirect Costs**

The indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

A series of one-way sensitivity analyses was undertaken to assess the sensitivity of results to different assumptions and possible methodological limitations. The explored options were the provision of MgSO4 only to women with severe pre-eclampsia, the impact of MgSO4 being subsidised or provided at no-cost in low GNI countries, and the application of the overall trial RR to all three GNI categories. Also explored was the effect of using country-specific unit costs; the total cost estimates were re-calculated using the most comprehensive single series of unit costs within each GNI group and then applied to all other countries within that group.

**Estimated benefits used in the economic analysis**

As the RR was virtually identical in the high and middle GNI groups, these were combined into one estimate of 0.63 (95% CI: 0.40 to 1.00). Using this combined estimate for the high and middle GNI groups, the average absolute risk reduction per person was 0.0031, 0.0054 and 0.0235 in the high, middle and low GNI countries, respectively. The number of women with pre-eclampsia who needed to receive MgSO4 to prevent one case of eclampsia was 324 (95% CI: 122 to infinity) in high GNI countries, 184 (95% CI: 91 to 6,798) in middle GNI countries, and 43 (95% CI: 30 to 68) in low GNI countries.

**Cost results**
The mean treatment cost per woman receiving MgSO4 was $86 for high GNI countries, $17 for middle GNI countries, and $13 for low GNI countries. This analysis confirmed that the main component of the treatment cost was not the drug cost itself, but the cost of administration (77%, 82% and 62%, respectively).

For the high GNI group, the observed total cost per woman was $12,764 for those receiving MgSO4 and $12,926 for the control group. The corresponding costs for the middle GNI group were $1,460 (MgSO4) and $1,381 (control), respectively, and for the low GNI countries, $172 and $153.

There was no statistically significant difference in "other costs" or total cost between the intervention and the control arms in any of the GNI groups when analysing the observed and unadjusted cost data.

The regression adjusted total costs were $12,904 for the intervention group and $12,839 for the control group for high GNI countries, $1,429 and $1,416, respectively, for middle GNI countries, and $168 and $157 for low GNI countries.

Synthesis of costs and benefits
The cost per case of eclampsia prevented was $21,202 (95% CI: 3,407 to infinity) for high GNI countries, $2,473 (95% CI: 402 to 21,015) for middle GNI countries, and $456 (95% CI: 301 to 779) for low GNI countries.

If MgSO4 prophylaxis was given only to women with severe pre-eclampsia, it would approximately half the cost per case of eclampsia prevented in all three GNI groups. A similar effect would result if MgSO4 was available at little to no cost in low GNI countries. The best-case scenario was free MgSO4 given only to women with severe pre-eclampsia in low GNI countries, for which the health care cost per case of eclampsia prevented was $121.

Application of the overall trial RR for eclampsia, instead of the values in the GNI categories, significantly decreased the cost-effectiveness estimate and the uncertainty around the ICER in high ($11,149, 95% CI: 711 to 85,146) and middle ($1,316, 95% CI: 435 to 2,879) GNI countries, but significantly increased them in low GNI countries ($638, 95% CI: 399 to 1,153). The application of a single series of unit costs in each GNI group did not significantly affect the results.

Authors' conclusions
Magnesium sulphate (MgSO4) for pre-eclampsia costs less and prevents more eclampsia in low gross national income (GNI) countries than in high GNI countries. Most of the treatment costs for MgSO4 came from its administration rather than the purchase price of the drug itself. Consequently, the variation in estimates of treatment cost between the three GNI country groups was largely explained by variation in labour costs and the local availability of specialist health care facilities. Cost-effectiveness substantially improves if MgSO4 is used only for severe pre-eclampsia, or the purchase price is reduced in low GNI countries.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used. It reflected standard clinical practice in the countries selected. You should judge whether this prophylaxis intervention is relevant in your setting, or whether other comparators from other commonly used drugs could have been relevant as well.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised placebo-controlled trial, which was adequate for the study question. Since the study was conducted alongside a parent clinical trial, that had already been published (The Magpie Trial Collaborative Group, 2002), the authors did not report full details of the effectiveness evidence.

Validity of estimate of measure of benefit
The number of cases of eclampsia prevented was chosen as the outcome measure for the present analysis because it was the main clinical outcome on which MgSO4 had an effect. In addition, it was a good surrogate for both maternal and
baby cause-specific mortality. The authors pointed out that using quality-adjusted life-years or disability-adjusted life-years would have required making assumptions about the health-related quality of life of women with pre-eclampsia, unsupported by evidence.

**Validity of estimate of costs**
The analysis of the costs was performed from a country-specific health service perspective. Therefore, the indirect costs were appropriately not included. Although some costs could have been omitted from the analysis, especially those falling on other agencies (e.g. community health and social care), these would be unlikely to affect the authors’ conclusions since they would improve the cost-effectiveness ratio.

To estimate the total direct costs, the authors considered all relevant cost categories. The variation among the different countries in relation to the use of resources might affect the authors’ conclusions, especially since some of the costs were considered globally. However, sensitivity analyses and statistical analysis of the costs were reported and 95% CIs were calculated. The price year was reported, which will aid future reflation exercises. Discounting was not necessary since the study had a very short-term time horizon.

**Other issues**
The authors stated that, as far as they were aware, no comparable economic evaluation had been conducted alongside a trial with so many participating countries and from such a diverse range. The prospective design of the economic evaluation, the pragmatic approach of the clinical study, and the diversity of the participating countries were likely to extend both the internal and external validity of the results. The authors' conclusions reflected the scope of the analysis. In view of the population and countries selected, the issue of generalisability was addressed. The authors stated that although MgSO4 is clinically effective, questions remain about the optimal dose and duration of therapy when used for pre-eclampsia. These questions have implications, not only for the benefits and risks of the treatment but also for its cost-effectiveness.

**Implications of the study**
There is a potential opportunity for international organisations and charitable foundations to make MgSO4 available at little or no cost to the health services in low GNI countries, where the problems associated with eclampsia and the clinical benefits of MgSO4 in pre-eclampsia are greatest and the price of MgSO4 is an important component of the treatment costs. Cost-effectiveness for the health services would be substantially improved in all countries by considering MgSO4 only for women with severe pre-eclampsia.

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