Institution: The University of Oxford

Unit of Assessment: 2

Title of case study

EVIDENCE BASED TREATMENT AND PREVENTION OF ECLAMPSIA

Summary of the impact

International obstetric practice has been changed by two large randomised controlled trials led from the University of Oxford's National Perinatal Epidemiology Unit, which demonstrated the efficacy of magnesium sulphate for both treatment and prevention of eclampsia during pregnancy, a condition characterised by fits in association with hypertension, and an important cause of maternal morbidity and mortality. Until the 1990s there was widespread geographical variation in the management of the condition, with magnesium sulphate used almost exclusively in North America. Following the publication of the results of these two trials magnesium sulphate is now in routine use globally, widely recommended in guidelines, and has been placed on the WHO Model List of Essential Medicines.

Underpinning research

Eclampsia represents the gravest end of the spectrum of hypertensive disorders in pregnancy. Usually preceded by pre-eclampsia, eclampsia is characterised by grand mal seizures, coma, hypertension, proteinuria and oedema, and can lead to maternal death. In 1992, with 383 affected women nationally, an Oxford-led study demonstrated that the rate of eclampsia was 5 per 10,000 women delivering in the UK. One in 50 of these affected women died from the disorder [1]. During this period eclampsia was a leading cause of maternal morbidity and mortality globally, responsible for an estimated 50,000 maternal deaths annually worldwide. Standard treatment at that time in the UK and many other countries was with an anticonvulsant such as diazepam or phenytoin, whereas in North America, magnesium sulphate was principally used. Clinicians elsewhere were sceptical about the efficacy of magnesium sulphate as there was insufficient randomised controlled trial evidence to support its use.

In 1995, the Collaborative Eclampsia trial of magnesium sulphate for the treatment of women having an eclamptic fit was led by Dr Lelia Duley and co-ordinated from the National Perinatal Epidemiology Unit (NPEU), University of Oxford. In this international multi-centre randomised controlled trial, conducted in nine countries, 1,687 women having an eclamptic fit were randomised to receive magnesium sulphate, diazepam or phenytoin [2]. The trial demonstrated a statistically significant halving in the recurrence of seizures for women treated with magnesium sulphate compared with diazepam and phenytoin. There were also non-significant reductions in maternal mortality, severe maternal morbidity, and fetal and neonatal effects.

The Oxford-led 'Magpie Trial', published in 2002, was a multi-centre international randomised controlled trial of magnesium sulphate for the prevention of eclampsia. This trial also demonstrated the benefits of magnesium sulphate in halving the risk of eclampsia in women with pre-eclampsia who were treated with magnesium sulphate [3]. In the absence of an existing preventive therapy, 10,141 women with pre-eclampsia across 33 countries were randomised to receive either magnesium sulphate or placebo. A cost-effectiveness study was subsequently conducted, using the Magpie Trial data. This demonstrated that the number of women with pre-eclampsia who needed to be treated to prevent one case of eclampsia was 324 in high resource settings, 184 in medium and 43 in low resource settings [4]. When treatment was used for severe pre-eclampsia the incremental cost (that is the amount of additional spending on magnesium needed) of preventing one case of eclampsia was $12,942 in high resource settings, $1,179 in medium resource settings and $263 in low resource settings.

A national study conducted by the NPEU in 2005 demonstrated a halving in the observed incidence of eclampsia in the UK following the introduction of magnesium sulphate treatment for severe pre-eclampsia, with a two-thirds reduction in the incidence of the associated severe maternal morbidity [5]; the effect sizes were at the level predicted by the original Eclampsia Collaborative and Magpie trials.

References to the research

[1]. Douglas KA, Redman CW. Eclampsia in the United Kingdom. Br Med J 1994;309:1395-400. doi: 10.1136/bmj.309.6966.1395.
PubMed ID: 7819845. ***This paper reports the first UK national study estimating the incidence of eclampsia prior to the publication of the eclampsia trials and is provided for background.***

[2]. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995; 345: 1455-63.
PubMed ID: 7769899. ***The first of two key papers, the* Collaborative Eclampsia Trial *demonstrates the clinical effectiveness of magnesium sulphate for the treatment of eclampsia compared with standard treatment.***

[3]. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, Smith D, Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877-90.
PubMed ID: 12057549. ***This is second of the two key papers and demonstrates the clinical effectiveness of magnesium sulphate for the prevention of eclampsia compared with placebo.***

[4]. Simon J, Gray A, Duley L; Magpie Trial Collaborative Group. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial. Br J Obstet Gynaecol 2006;113:144-51.
PubMed ID: 16411990. ***This paper reports the economic evaluation demonstrating the particular value of treatment in low resource settings.***

[5]. Knight M on behalf of UKOSS. Eclampsia in the United Kingdom 2005. BJOG. 2007;114(9):1072-8.
PubMed ID: 17617191. ***This paper reports the second and most recent UK national study estimating the incidence of eclampsia following the introduction of magnesium sulphate into clinical practice for the prevention and management of eclampsia and is provided to complete the picture of evidence.***

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Details of the impact

National Impact:
The Royal College of Obstetricians & Gynaecologists incorporated the findings into their clinical guidelines (2006) for the management of both severe pre-eclampsia and eclampsia, and these continued to be the national guidance followed until 2010 [A]. This guidance was superseded by NICE guidelines which cite the studies and recommend use of magnesium sulphate for treatment of both eclampsia and severe pre-eclampsia [A]. We estimate that two hundred cases of eclampsia per year are now prevented in the UK amongst an estimated 40,000 pre-eclamptic women treated with magnesium sulphate, and whilst deaths do occur, they are now extremely rare [B].

Global Impact:
WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia recommend magnesium sulphate for the prevention and treatment of eclampsia, specifically citing these studies [C]. Other national guidelines in high resource countries also cite the studies while making the same recommendations [D]. The *Pre-Eclampsia/Eclampsia: Prevention, Detection and Management toolkit for Developing Countries* was developed by the USAID-funded Maternal and Child Health Integrated Program (MCHIP) as a resource of current evidence, materials and experiences from around the world and cites the studies as the key evidence behind the recommendation to use magnesium sulphate for the prevention and treatment of pre-eclampsia and eclampsia [E].

A recent systematic review [F] demonstrated that in Bangladesh, India, Pakistan, and Nigeria in addition to the UK, the introduction of treatment for eclampsia with magnesium sulphate as a result of these trials consistently results in a halving of the rates of maternal death. Magnesium sulphate is now included on the WHO Model List of Essential Medicines [G] and was recently added to the Interagency Emergency Health Kit of recommended medicines and medical devices for 10,000 people for approximately three months [H].

Magnesium sulphate continues to be introduced in low resource countries internationally, as part of initiatives aimed at reaching Millennium Development Goal 5, to reduce maternal mortality by three-quarters by 2015. For example, a recent Department for International Development intervention in Tanzania included the provision of magnesium sulphate as one of four key actions [I].

Sources to corroborate the impact

[A]. NICE Guideline CG107 (issued August 2010). The management of hypertensive disorders during pregnancy. http://www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf [Accessed 6/9/2013]. ***This is the current UK national guidance recommending use of magnesium sulphate to prevent eclampsia and referencing the studies in the supporting evidence. See section 1.8.***

[B]. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, et al. (2011) Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 118 Suppl 1: 1-203. PubMed ID: 21356004. ***This reports cases of maternal death in the UK and shows the rarity of deaths from eclampsia. It nevertheless cites the Oxford University research to emphasise the importance of magnesium sulphate to prevent eclampsia. See pages 68 & 70.***

[C]. WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia (2011). http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf [Accessed 06/09/2013]. ***WHO guidance recommending magnesium sulphate for the management and prevention of eclampsia. See pages, 2, 20-24.***

[D]. Society of Obstetricians and Gynecologists of Canada Clinical Practice Guideline. Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy (2008). http://sogc.org/wp-content/uploads/2013/01/gui206CPG0803hypertensioncorrection.pdf [Accessed 06/09/2013]. ***An example of a national guideline also recommending magnesium sulphate for the management and prevention of eclampsia. See sections S5 & S32.***

[E]. Pre-Eclampsia/Eclampsia: Prevention, Detection and Management toolkit (2011) http://archive.k4health.org/sites/default/files/PEE%20Bibliography%20nov2011_0.pdf *[*Accessed 28/10/2013]. ***A toolkit for developing countries highlighting the importance of magnesium sulphate for preventing and treating eclampsia and pre-eclampsia for developing countries.***

[F]. McDonald SD, Lutsiv O, Dzaja N, Duley L. A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use. Int J Gynaecol Obstet. 2012;118(2):90-6.
PubMed ID: 22703834. ***This systematic review identifies studies documenting the efficacy of magnesium sulphate in "real-life" cohort studies and shows a consistent halving in maternal death amongst women with eclampsia treated with magnesium sulphate.***

[G]. WHO Model List of Essential Medicines (2011).
http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf [Accessed 06/09/2013]. ***WHO list of recommended essential medicines for health services listing magnesium sulphate for the treatment of eclampsia and management of severe pre-eclampsia. See p 4.***

[H]. WHO Interagency Emergency Health Kit (2011).
http://whqlibdoc.who.int/publications/2011/9789241502115_eng.pdf [Accessed 06/09/2013]. ***Details of WHO Interagency Emergency Health Kit 2011 - Medicines and medical devices for 10,000 people for approximately three months. Magnesium sulphate included in 2011 version for treatment of eclampsia/pre-eclampsia. See page 6.***

[I]. Department for International Development (2011). Business Case and Intervention Summary - Reproductive and Maternal Health Supplies in Tanzania.
http://devtracker.dfid.gov.uk/projects/GB-1-202959/documents/ [Accessed 06/09/2013]. ***This describes the DFID intervention for 2012-14 in Tanzania, citing the Magpie study as evidence for the provision of magnesium sulphate to prevent maternal death. See Evidence section - Clinical effectiveness of maternal health supplies.***