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Our article does not recommend to use any sequential method or to use push method first and then reverse breech extraction. We have discussed other authors' views in the discussion section. The full paragraph reads: 'The question as to which of the methods for delivering the impacted head at full-dilation caesarean section is the safest, and whether there is a role for the sequential use of these techniques, remains unanswered. The suggested approach is to use the push method first and then the reverse breech extraction if it is difficult to deliver the head. It is, however, unknown if these manoeuvres will have an additional beneficial or an additive detrimental effect.[2] Limited evidence suggests that the reverse breech extraction is associated with significantly fewer maternal complications, but the challenge is a lacuna (or gap) in training, as more than half of trainees are not confident in reverse breech extraction.'[3]

We discussed the view expressed by Blickstein to use the push method first and then the reverse breech extraction but it is not known whether that will be beneficial or detrimental. Although evidence supports reverse breech extraction technique, there is a huge gap in training.[3] Our meta-analysis of included studies shows beneficial effects of reverse breech extraction. Therefore we uphold our original conclusion that the reverse breech extraction technique for delivery of a deeply impacted fetal head in second-stage caesarean section carries a significantly lower risk of extension of the uterine incision, lower risk of infection, is quicker, and is associated with less operative blood loss as compared with the push method. There is an urgent need to develop trainees' skills with these methods to deliver the impacted fetal head, and thus reduce complications. ■

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Re: Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia: a systematic review

Clinical pharmacokinetics of low-dose magnesium sulphate regimens for eclampsia in low-resource countries: does it matter?

Sir,

The systematic review by Okusanya et al.[1] stimulated us to put forward a few comments regarding the clinical pharmacokinetics of low-dose magnesium sulphate, which is now widely used in many low-resource countries.[2–4] Although magnesium sulphate is a life-saving drug for the treatment of eclampsia it is potentially toxic, occasionally leading to fatality. Unfortunately, the minimum therapeutic serum level of magnesium is never explored rigorously as it is often performed in microbiological studies. This has led to a generally held view of its effective therapeutic level (2.0–3.5 mmol/l) and 'narrow therapeutic index'.

Two commonly used regimens, i.e. Pritchard and Zuspan, administer 39 and 28 g of magnesium sulphate, respectively, in the first 24 hours, and yet yield comparable efficacy, despite the lower serum level of magnesium in the Zuspan regimen.[1] Interestingly, the index review clearly demonstrated that in both regimens the serum magnesium levels were falling short of the so-called therapeutic window, and succeeded in refuting the long-held perception about the effective therapeutic level.[1]

Volume distribution and consequently the serum concentration of a drug both depend on maternal weight, which is lower on average in developing countries compared with western countries (45 versus 65 kg, respectively). Currently, in many low-resource countries with lower average maternal weight, low-dose magnesium sulphate regimens (a total dose of 20.5–22.5 g in the first 24 hours) have been tried, with low case fatality and fewer recurrences of seizures.[2–4] The mean total dose of magnesium sulphate administered per patient was significantly less compared with the Pritchard regimen (40.0 versus 23.9 g; $P < 0.001$).[2] Pharmacokinetic data with the low-dose regimen used in India and Bangladesh demonstrated that a lower steady-state level of magnesium (approximately 1.4 mmol/l) was adequate to control maternal seizures;[3,4] however, it is alarming that 'absent knee jerk', an early sign of magnesium toxicity, was also noted with a mean magnesium level of 1.37 mmol/l (range 1.23–1.56 mmol/l).[3] Thus in low-resource countries, which contribute a major burden of eclampsia, there was an overlap between the steady-state level of the drug and the appearance of clinical toxicity, even with a low-dose magnesium regimen. Therefore, the clinicians must remain vigilant. Furthermore, although the lower average maternal weight in low-resource countries favours the reduction of magnesium

sulphate dose, obesity, especially in western countries, may tilt the balance in the opposite direction.

In conclusion, the current pharmacokinetic evidence suggests that, as affirmed by the reviewers, the therapeutic level of magnesium sulphate for seizure control is much lower than was suggested in early studies. Therefore, the low-dose regimen should be widely tried along with pharmacokinetic studies in low-resource countries with lower average maternal weight. Moreover, there could be a qualitative effect of the drug, as the magnesium ion works through more than 300 enzymes in the human body, and the quantity required may be very small. This hypothesis, however, requires rigorous exploration with basic research. Although we highly commend the authors' effort to enrich us with a succint synthesis of otherwise incomprehensible scattered data addressing an important clinical issue, further information could be gleaned from the existing literature. ■

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Authors' reply

Sir,

We thank Narayan Jana and colleagues for their positive comments on our systematic review.[1] Their comments further emphasise the need to revisit an age-long belief regarding the therapeutic range of magnesium sulphate ($MgSO_4$) for eclampsia prophylaxis and treatment. We agree that our findings challenged the fundamental notion that serum magnesium concentration of 2 mmol/l is the minimum level that must be achieved before $MgSO_4$ can be protective against eclamptic seizures. Although these findings lend some credence to the clinical use of low-dose regimens, we wish to caution that the relationship between serum magnesium concentration attained by any particular $MgSO_4$ regimen and the observed clinical effect may not be that straightforward, and general statements on the comparative efficacy of a low-dose regimen based on small trials may be misleading.

Although the fundamental hypothesis of clinical pharmacokinetics is that a quantitative relationship exists between the pharmacological effects of a drug and its plasma concentration, there are exceptions. For some drugs, no clear or simple relationship exists between pharmacological effects and plasma concentration.[2] In our view, the pharmacokinetic and clinical evidence available so far does not support a clear relationship between serum magnesium concentration and observed clinical effects, and without a standard exposure–response study, it would be too early to confidently attribute clinical efficacy to any particular serum concentration. This assertion is supported by reports of clinical efficacy among pre-eclamptic women with lower serum magnesium concentrations, and clinical failure among those with concentrations within the so-called therapeutic range.[3]

It is true that that the volume of distribution is a critical pharmacokinetic parameter that should dictate the adjustment of dosage in an individual woman; however, it is important to note that the volume of distribution does not depend only on weight, and can differ according to other variables such as age, body composition, and presence of disease.[2] Recommending low-dose $MgSO_4$ regimens solely on the basis of lower maternal weight ignores the relevance of these variables and other important pharmacokinetic parameters that differ between women and settings. For instance, $MgSO_4$ clearance (which could vary by disease severity) and its bioavailability (which depends on administration route) compound an assumption of a linear relationship between maternal weight and serum magnesium concentration.

In spite of the common use of a low-dose $MgSO_4$ regimen in settings where women are generally of smaller size, current evidence from systematic reviews is insufficient to conclude that such a regimen fairs better than standard regimens in terms of efficacy and side effects.[4,5] In the absence of clear evidence demonstrating clinical non-inferiority of low-dose regimens compared with the standard (Pritchard or Zuspan) regimens, we do not agree that a low-dose regimen should be 'widely tried' in settings with lower maternal weight. Such inference would be contrary to the current WHO recommendation, which was based on the largest trials demonstrating efficacy of standard regimens. The WHO is