Single loading dose versus standard 24-hour magnesium sulfate in women with severe preeclampsia and eclampsia: A systematic review and metaanalysis*

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ABSTRACT

Objectives: The primary goal of this study is to determine if a single loading dose of Magnesium sulfate (MgSO4) is comparable to standard 24 hour therapy in preventing seizures with severe preeclampsia and eclampsia

Study Design: Metaanalysis and Systematic review of six randomized controlled trials

Patients/Subject Selection: Patients diagnosed with severe preeclampsia and eclampsia

Intervention: Giving of single loading dose only (study group) versus 24-hour $MgSO_4$ therapy (control) in patients with severe preeclampsia and eclampsia

Outcome Measures: (1) Anti-convulsant effects (2) Maternal: loss of deep tendon reflex and oliguria, incidences of caesarean section, Hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, post partum hemorrhage and intensive care unit admissions and (3) Neonatal complications: incidences of neonatal intensive care unit (NICU) admission, APGAR score at 5 minutes and death

Results: Occurrence of seizures was similar in both groups. The risk difference of -0.00 (95% Confidence interval (CI): -0.04 to 0.03; p=0.84) showed no significant difference and the combined studies were found to be homogenous with an I^2 of 0.0.

Conclusion: A single loading dose of MgSO4 is comparable in preventing seizures of preeclamptic and eclamptic patients with similar maternal and neonatal complications except for a lesser occurrence of decreased patellar reflex in the study group (p=<000001).

Keywords: Preeclampsia, Eclampsia, Single Loading Dose, 24-hour regimen

INTRODUCTION

Background of the Study

Preeclampsia in pregnancy remains the most common medical disorder complicating 2-5% of all pregnancies in the Philippines[1] and 10 % worldwide.[2] Together with eclampsia, both belong in the top three causes of maternal death globally[3] of which ninety-nine percent occur in low to middle income countries.[4] Both contribute as the most significant cause of maternal and perinatal morbidity and mortality needing sufficient prenatal follow-up and delivery plans to prevent adverse outcomes and maximize financial capabilities.

Preeclampsia is defined as a pregnancy-specific multisystem disorder, characterized by new-onset hypertension and proteinuria after 20 weeks age of gestation.[5] Specifically, severe features include any of the following in absence of proteinuria: 1) Resting systolic blood pressure of > 160 mmHg, or a diastolic blood pressure of > 110 mmHg on 2 occasions at least 4 hours apart 2) Thrombocytopenia (<100,000 cells/uL), 3) Impaired liver function, severe persistent right upper quadrant or epigastric pain unresponsive to medications and not accounted for by alternative diagnosis, or both 4) Progressive renal insufficiency 5) Pulmonary edema

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and 6) New onset cerebral or visual disturbances[2]. Severe preeclampsia may progress to eclampsia requiring need for anti-convulsants. Until today, magnesium sulfate ($MgSO_4$) still remains the drug of choice in controlling and preventing recurrent convulsions with established superiority over diazepam and phenytoin. Its use reduced maternal deaths from 7% to 4% and recurrent rate of convulsion by 52% and 67% when compared with diazepam and phenytoin respectively.[6]

Description of intervention

Magnesium sulfate was administered via Pritchard method of a 4 gram intravenous bolus (IV) plus 5 grams intramuscular doses on alternating buttocks.

How the intervention might work

Belonging in a third world country like the Philippines, diagnosis of preeclamptic and eclamptic patients is usually late due to conservative means of management. Problems of late referrals to tertiary hospitals is also common hence patients are usually received in severe condition. Lack of hospital staff in terms of monitoring (regulating the intravenous line, urinary output, vital signs, examining MgSO4 toxicity) also posts an issue.

Rationale of the Study

Magnesium sulfate being the standard drug of choice for pre-eclampsia and eclampsia accompanies disadvantages such as close monitoring for dose related toxicity in terms of urine output, respiratory rate and tendon reflexes. Each should be well observed by health care personnel which may also indirectly increase total cost and time spent in patient management. Pain and flushing are common reasons for discontinuance of treatment hence reduction of duration of therapy, frequency of monitoring will enhance not only patient-hospital satisfaction but also promote early patient ambulation and newborn care. According to the systematic review of Duley, although strong evidence supports the use of $MgSO_4$, trials comparing alternative regimens are too small for reliable conclusions[7] hence lead the researchers to find out if a single loading dose of $MgSO_4$ would be able to control severe pre-eclampsia and eclampsia without compromising the effectivity of the drug especially in low-resource countries.

Research Question

Is single loading dose of MgSO4 comparable to standard 24 hour regime in preventing seizures with severe preeclampsia and eclampsia?

Research Hypothesis

H0: There is no significant difference between the single loading dose and 24- hour MgSO4 in preventing seizures with severe preeclampsia and eclampsia

Hi: There is a significant difference between the single loading dose and 24- hour MgSO4 in preventing seizures with severe preeclampsia and eclampsia.

OBJECTIVES

The primary goal of this study is to determine if single loading dose of MgSO4 is comparable to standard 24 hour therapy in preventing seizures with severe preeclampsia and eclampsia. Specifically, this study aims to compare the following secondary outcomes:

Maternal outcomes

a. $MgSO_4$ toxicity: loss of patellar reflex and oliguria
b. Manner of delivery: Cesarean Section
c. Progression to HELLP syndrome
d. Post Partum Hemorrhage
e. Maternal Intensive Care Unit (MICU) admission

Neonatal outcomes

a. Nursery Intensive Care Unit (NICU) admission
b. APGAR Score at 5 minutes (Low= < 7, High= >7)
c. Mortality

REVIEW OF THE RELATED STUDY

Hypertensive disorders in pregnancy specifically preeclampsia and eclampsia are most common in low to middle-income countries[7] due to poor prenatal quality of care and non-compliance to prescribed hypertensive drugs. Up to date, $MgSO_4$ remains the standard therapy for both prevention and control of seizures despite its toxicity and administration and monitoring difficulty.[3,8] The collaborative eclamptic trials of 19959 showed that $MgSO_4$ is superior compared to diazepam or phenytoin in reducing both maternal mortality rate and convulsion recurrence. Reducing $MgSO_4$ toxicity without compromising its efficacy in controlling seizures and lowering mortality rates remain a major challenge.[10]

Several studies[7,11,12] have already been done to identify the minimum effective dose of $MgSO_4$ without compromising the effectivity of the drug however, a recent Cochrane review[7] also failed to reach a conclusion due to the small number of available trials. A recent randomized controlled trial[13] mentioned that a shortened (6-hour) postpartum regimen was sufficient as alternative to standard 24-hour seizure prophylaxis for women at low risk for eclampsia however, a larger number of subjects was also suggested. Another study involving patients with pre-eclampsia found that median treatment duration was 4 hours for all groups with no cases of eclampsia recorded.[14]

Elkahyat did a double blind randomized controlled trial involving 240 women and demonstrated that even a

single loading dose was comparable versus the standard treatment. It showed decreased number of patient follow-ups without increase in complications and avoided possible side effects of MgSO4.[15] Another trial using only loading dose regime found that there was also no significant difference in terms of perinatal outcome and seizure occurrence after a week follow-up.[16]

For the maternal outcomes (morbidity/ mortality), a randomized controlled trial[17] involving 126 preeclamptic and eclamptic women showed comparable results however further investigation was suggested to determine the most effective dosage for patients with lower body mass indeces.

Regarding the neonatal outcomes, results still depend on the severity of: Intrauterine growth retardation (IUGR), gestational age, birth weight and capability of NICU facility and not on the duration nor MgSO4 administered.[10]

With these, the researchers determined whether a single dose of $MgSO_4$ was sufficient compared to standard 24-hour regime benefitting low to middle-income countries with inadequate facilities where even lower doses of $MgSO_4$ administered can prevent seizures prior to transfer to bigger hospitals.

METHODOLOGY

A. Criteria for considering studies for this review

Type of study

Randomized controlled trials comparing single loading dose of MgSO4 to standard 24 hour regime in women with pre-eclampsia and eclampsia were included in the study. Cross-sectional, Case-control or Quasi-randomized studies were disregarded.

Participants

Woman diagnosed with severe pre-eclampsia and eclampsia at any time of pregnancy were included. Those who received MgSO4 or anticonvulsants prior to treatment were excluded as well as those with co-morbidites such as diabetes mellitus, thyroid diseases and other neurological disorders. Patients with HELLP syndrome, whether partial or complete were excluded.

Interventions

Studies comparing single loading dose and 24 hour doses of $MgSO_4$ as anti-convulsant in severe preeclampsia and eclampsia were used.

Outcome Measures

The primary outcome of interest is occurrence of convulsions after completion of assigned MgSO4 therapy. Secondary outcomes are the following: Maternal outcome- a) $MgSO_4$ toxicity in terms of: loss of patellar reflex and oliguria b) MICU admission c) Manner of delivery: Cesarean Section d) Progression to HELLP and e) Post Partum Hemorrhage. Neonatal outcome- a) NICU admission b) Apgar Score at 5 minutes (Low=< 7, High= >7) c) Mortality

B. Search strategy for identification of studies

The Preferred Reporting Items for Systematic reviews and Meta – Analyses (PRISMA) guidelines for metaanalysis of randomized controlled trials was used in this study. The researchers used the following computerized databases for english language publications using the terms: “Loading Dose” versus “Standard” “Magnesium Sulfate”, “Preeclampsia”, and “Eclampsia” and their related subject headings: Clinical Key, PubMed, OVIDSP, Researchgate, Cochrane Center Register of Controlled Trials, HERDIN, EHBSCO and Google scholar from 2010 up to December 2016. No additional limits nor filters were placed to maximize sensitivity of search.

C. Study selection

Randomized controlled trials including single loading dose of Magnesium sulfate used as anti-convulsant in eclampsia and severe preeclampsia compared with standard 24-hour dose were included. Independent reviews of database search results was done and disagreements were resolved by consensus among the authors. Published abstracts of journals which additional information cannot be extracted were excluded. Authors of selected publications were contacted via electronic mail for their approval regarding the use of their study and complement data if necessary.

D. Data extraction and management

Titles and abstracts of each journals were screened for relevance. Full text of studies fulfilling the eligibility criteria were included for qualitative assessment by 3 independent authors using the following areas:

1. Were the criteria for diagnosing preeclampsia and eclampsia stated clearly? (Score: Yes= 1; No=0)
2. Was an experimental design used? (Score: Randomized controlled trial with defined protocol =2; Protocol only =1; None=0)
3. Was there follow-up in all patients? (Score: Yes =1; None =0)
4. Was blinding done on the part of the health personnel, patients and treatment outcomes? (Score: Health personnel and treatment outcomes clear =2, Health personnel or treatment outcomes only =1, None =0)

Risk of biases in individual studies

Once publications were selected, quality was assessed independently by the three authors to ensure validity of each included trial. Criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions was used. Each study was evaluated in terms of Directness, Validity, Quality of concealment of allocation, Blinding, Applicability, and Completeness of follow-up. Risk of bias assessment in each study was done using the following scale and interpretation:

A - Low risk bias: Plausible bias unlikely to seriously alter the results where all the criteria are met
B - Moderate risk bias: Plausible bias that raises some doubts about the results where one or more criteria partly met
C - High risk bias: Plausible bias seriously weakens confidence in the results where one or more criteria not met

Selection Bias (Randomized and allocation concealment)

Concealment of allocation was assessed using the following criteria:
Adequate: If concealment of allocation, such as telephone randomization, numbered, sealed, opaque envelopes were used.
Unclear: Unclear whether concealment of allocation was adequate;
Inadequate: If concealment of allocation such as open random number tables, sealed envelopes that are not numbered nor opaque.

*If the method of allocation concealment was unclear, authors were contacted to provide further details.

Performance Bias

Blinding was assessed if adequate in the following criteria:
Participants: Yes/no/unclear or unspecified
Caregiver: Yes/no/unclear or unspecified
Outcome: Yes/no/unclear or unspecified

Detection

Blinding of outcome assessment done using the following criteria:
Follow-up clear: If blinding was stated clearly
Unclear: If there were no stated procedure of blinding
Inadequate: If blinding of outcomes was not possible

Attrition Bias (Loss of participants)

Completeness of follow up was assessed by:
Complete: If < 5% of participants were excluded from the study
Incomplete: If 5% to 10% of participants were excluded from the study
Inadequate: If > 10% of participants were excluded from the study

Completeness of outcome
Complete: If all objectives were answered in the conclusion
Incomplete: If some objectives were answered in the conclusion

Measurement of Treatment Effect

Metaanalysis statistical analyses were done using the Review Manager soft-ware: RevMan 2.0 of 2008. Results were presented as summary risk ratio with 95% confidence interval, as risk difference and number needed to treat if necessary.

Dealing with missing data

Data was analyzed for all participants in the group to which they were allocated. For those original reports with insufficient information, attempts were done to correct the group. For those with missing data, clarification from the authors were sought.

Assessment of heterogeneity

Heterogeneity (I^2) measures the variability observed between studies. An $I^2 < 25\%$ was considered homogenous, 25% to 75% as medium and >75% as high heterogeneity. The lower the I^2, the better the study and only up to 75% I^2 were considered. Conclusion of accuracy of estimates was difficult for $I^2 > 75\%$.

Estimation of Risk Difference

Statistical heterogeneity was assessed using Fixed and Random-Effects model. The Fixed-Effect Model was used for homogenous studies and Random-Effect for medium heterogeneity studies. Forest Plot was provided to illustrate visual summary of analysis and graphically represent estimates and confidence interval for each study.

Assessment of reporting Bias

Investigation on publication bias using funnel plots, was done to assess asymmetry.

E. Data synthesis
Subgroup analysis and investigation of heterogeneity

Substantial heterogeneity was investigated using subgroup and sensitivity analysis based on the severity of hypertensive disorder at trial entry: severe pre-eclampsia, eclampsia, unclear or mixed.

Sensitivity Analysis

Sensitivity analysis to determine effect of trial was carried out. Poor quality (mostly 'no' and 'unclear'

concealment of allocation or blinding) studies were excluded to assess any substantive difference to the overall result. Only main outcomes were used for the subgroup and sensitivity analyses.

Statistical analysis

Outcomes of single loading $MgSO_4$ compared with standard 24 hour treatment were analysed using RevMan software 2.0. The significance between groups was estimated by risk difference with 2 tailed 95% Confidence interval. Mantel and Haenzel and fixed-effects model were employed on the variables. P-value of <0.05 were considered significant.

RESULTS

A. Study selection

Figure 1 showed that from a total of 10, 753 records identified through database searching and applying inclusion and exclusion criteria, only six studies were left for qualitative assessment of the authors.

B. Quality assessment

All 6 included studies used similar subjective clinical criteria to identify patients with severe preeclampsia and eclampsia. Baseline characteristics were same in terms of age range, gravidity, systolic, and diastolic blood pressures however, age of gestation was not clearly specified. In the quality assessment, each had at least a score of 3 in the 4 areas.

RESULTS OF RESEARCH

Included studies

Six randomized control trials were included in the study. Each dealt with single loading dose of $MgSO_4$ comparing with the standard regime.

Excluded studies

Two studies were excluded from the list due to: Non-randomized control trial type of study, patients included preeclampsia with mild symptoms only.

RISK OF BIAS

Allocation (selection bias)

Five out of 6 studies had clear selection bias.

Blinding (performance and detection bias)

Regarding performance bias, all studies had moderate risk since blinding of patients and hospital personnel was not mentioned but possible despite contacting the respective authors of the included journals.

Incomplete outcome data (attrition bias)

There was complete data outcome in all studies.

Selective reporting (reporting bias)

The objectives, scope and limitations in all studies were clearly stated and met.

Other potential sources of bias

No other potential sources of bias noted.

DATA ANALYSIS

Table 1 showed the review of authors' judgements about each risk of bias item presented as percentages across all included studies and at least 75% are at low risk. Performance and Detection biases were unclear due to lack of authors's reply despite contacting them. Figure 2 showed the authors' review of the biases for each included studies. A funnel plot was also done and showed no publication bias among the studies as shown in Figure 3.

A. Primary Outcome

Figure 4-A showed that out of 1,040 patients of the 6 included studies combined, those given with single loading dose of $MgSO_4$ (28/423) had comparable eclamptic fit occurrence to those given with 24-hour therapy (45/617). The risk difference of -0.00 (95% CI: -0.04 to 0.03; p=0.84) showed no significant difference between the two groups and found to be homogenous with an I^2 of 0.0.

Figures 4-B and 4-C showed the subgroup analysis for seizure occurrence in severe preeclampsia and eclampsia respectively. Both revealed no significant difference between the study and control groups. In severe preeclampsia group, the risk difference is -0.00 (95% CI: -0.03 to 0.04; p=0.84) with and I^2 of 8%. In eclampsia group, the risk difference is -0.04 (95% CI: -0.15 to 0.07; p=0.44) with and I^2 of 0%. All 6 included studies were noted to be homogenous.

B. Secondary Outcome

Maternal outcomes

Regarding $MgSO_4$ toxicity of the 4 included studies in Figure 5-A, there was significantly less knee hyporeflexia occurrence in those given with single loading dose (4/330) compared to 24-hour regime (29/530). The risk difference of -0.10 (95% CI: -0.13 to -0.07; p<0.00001) favors the experimental group. The combined studies were found to be homogenous with an I^2 of 0.0.

Figure 5-B, showed no significant difference in oliguria occurrence between the study (15/330) and control groups (29/530) with risk difference of -0.05 (95% CI: -0.13 to -0.04; p=0.27) however heterogeneity was at 83%.

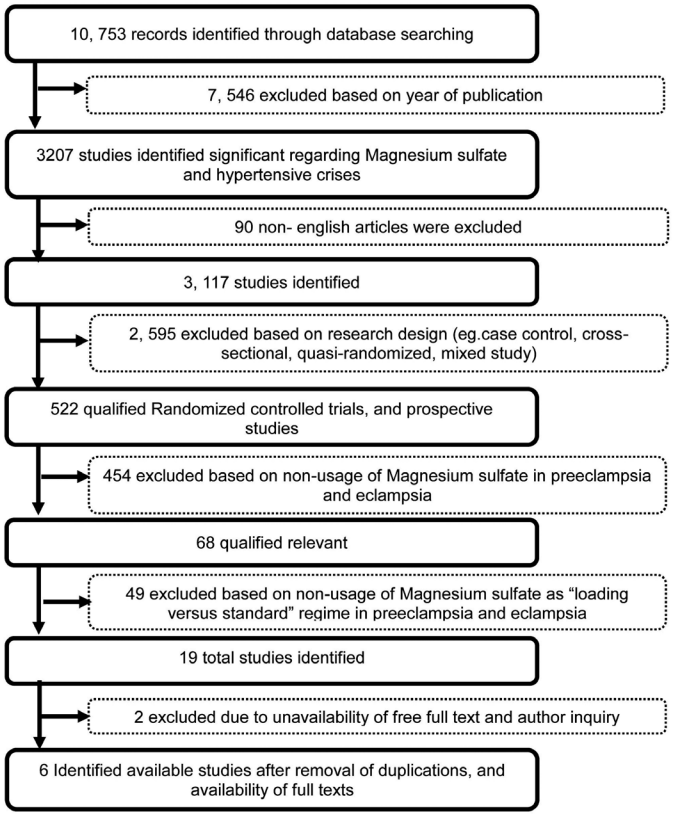

Figure 1. Flow diagram of studies selection process

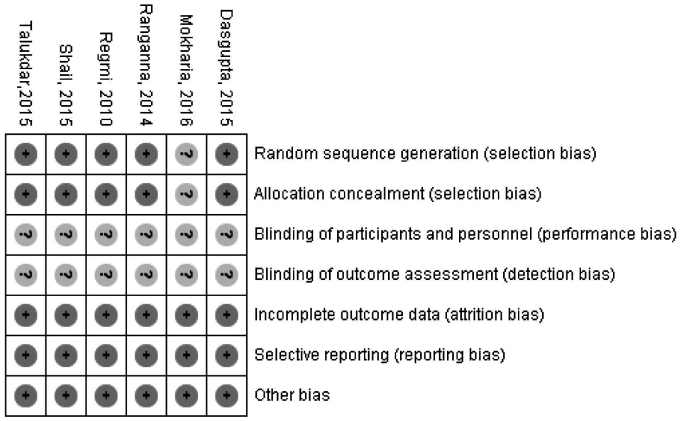

Figure 2. Risk of bias summary

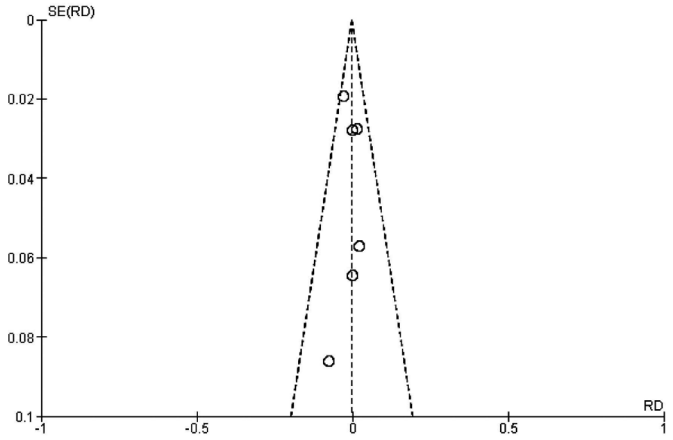

Figure 3. Funnel plot among included studies (Publication bias)

Figure 5-C revealed similar results on mode of delivery whether single loading dose (144/273) or 24-hour MgSO4 therapy (284/467). Risk difference was -0.06 (95% CI: -0.20 to 0.07; p=0.34) with medium heterogeneity of 55%.

Figure 5-D also showed no difference between study (4/100) and control (3/100) groups in the development of HELLP syndrome. Risk difference was 0.01 (95% CI: -0.04 to 0.06; p=0.70) with homogenous I^2 of 0%.

No predilection to post partum hemorrhage was established whether given single loading dose (4/100) or standard 24-hour therapy (5/100) as shown in Figure 5-E.

Risk difference was -0.01 (95% CI: -0.07 to 0.05; p=0.73) with homogenous samples at 6%.

Figure 5-F also showed similar results on MICU admission comparing single loading dose (17/193) and standard 24-hour therapy (24/387). Risk difference was -0.01 (95% CI: -0.14 to 0.12; p=0.85). There was medium heterogeneity at 59%.

Neonatal Outcomes

Same outcome went for the four combined studies in relation to NICU admission shown in Figure 5-G. Single loading dose (62/282) and standard 24-hour therapy (115/482) showed no significant difference. Risk difference was -0.05 (95% CI: -0.20 to 0.09; p=0.46) with high heterogeneity of 76%.

Figure 5-H showed no difference was found between study (10/82) and control (14/82) groups regarding APGAR Scores at 5 mins. Risk difference is -0.05 (95% CI: -1.16 to 0.06; p=0.38) with good homogeneity at I^2 at 0%.

Lastly, among 3 included studies, Figure 5-I showed that administration of whether single loading dose (11/252) or 24-hour MgSO4 therapy (15/452) had no effect in prenatal mortality. Risk difference was -0.01 (95% CI: -0.07 to 0.06; p=0.84) with medium heterogeneity of 56%.

DISCUSSION

Pritchard introduced MgSO4 for prevention of primary and recurrent seizures.[18] It was first suggested at 1906,[19] and remained the anticonvulsant of choice over diazepam and phenytoin. Its superiority was already determined in a multicentric randomized control trial[9] hence the question, "Why Magnesium sulfate?":

1. Vasodilatory effect with subsequent decrease in cerebral ischemia.[20]
2. N-methyl D-aspartate (NMDA) receptors blockade in seizure genesis and
3. Calcium channel blockade preventing cerebral vasospasm[21]

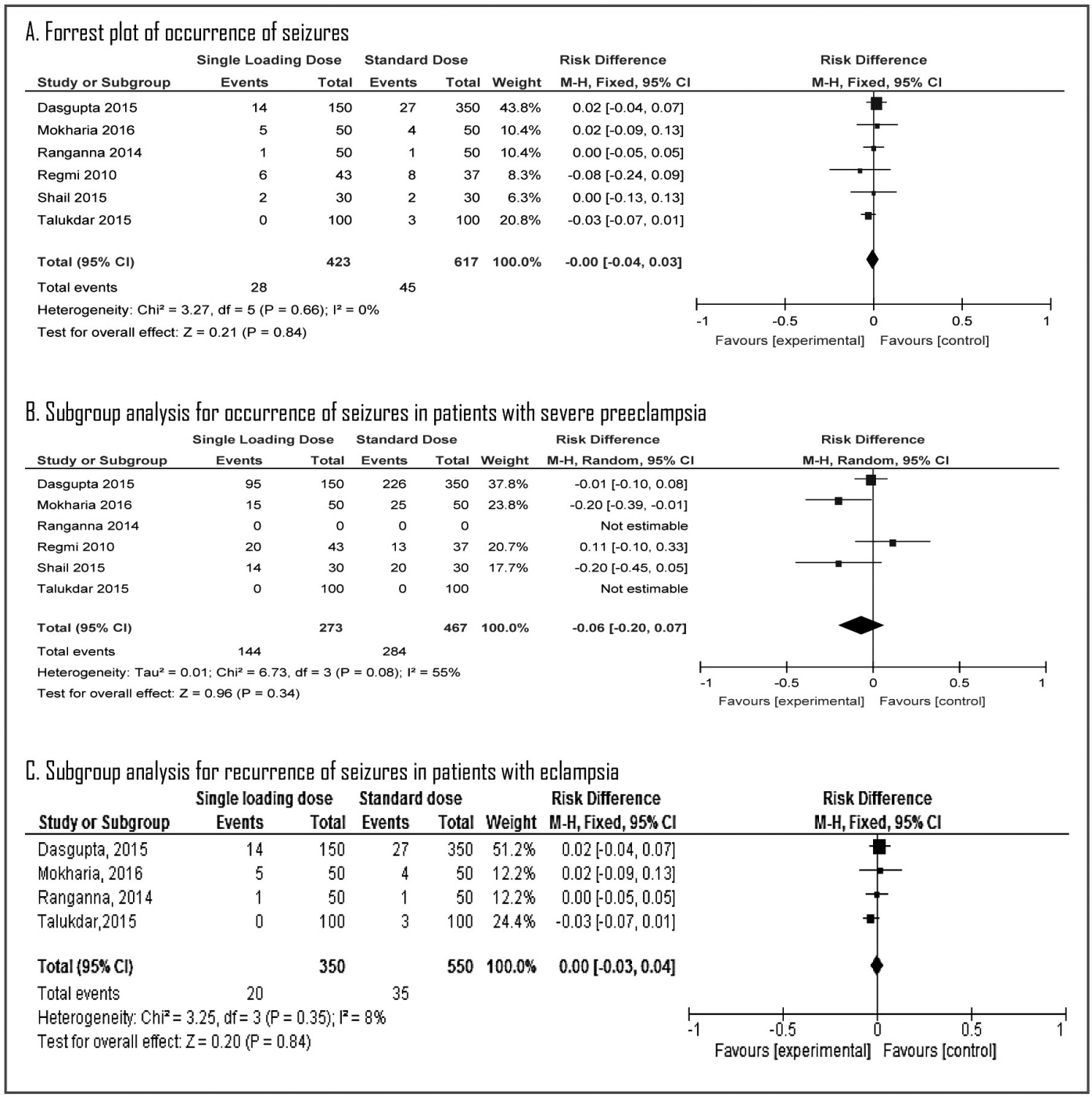

Figure 4. Forrest plots of primary outcomes

Table 1. Assessment of risk of biases of included studies

Study, year	Selection Bias	Allocation Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
Regmi, 2010	A	A	B	B	A	A
Sail, 2015	A	A	B	B	A	A
Talukdar, 2015	A	A	B	B	A	A
Ranganna, 2014	A	A	B	B	A	A
Dasgupta, 2015	A	A	B	B	A	A
Mokhaira, 2016	B	B	B	B	A	A

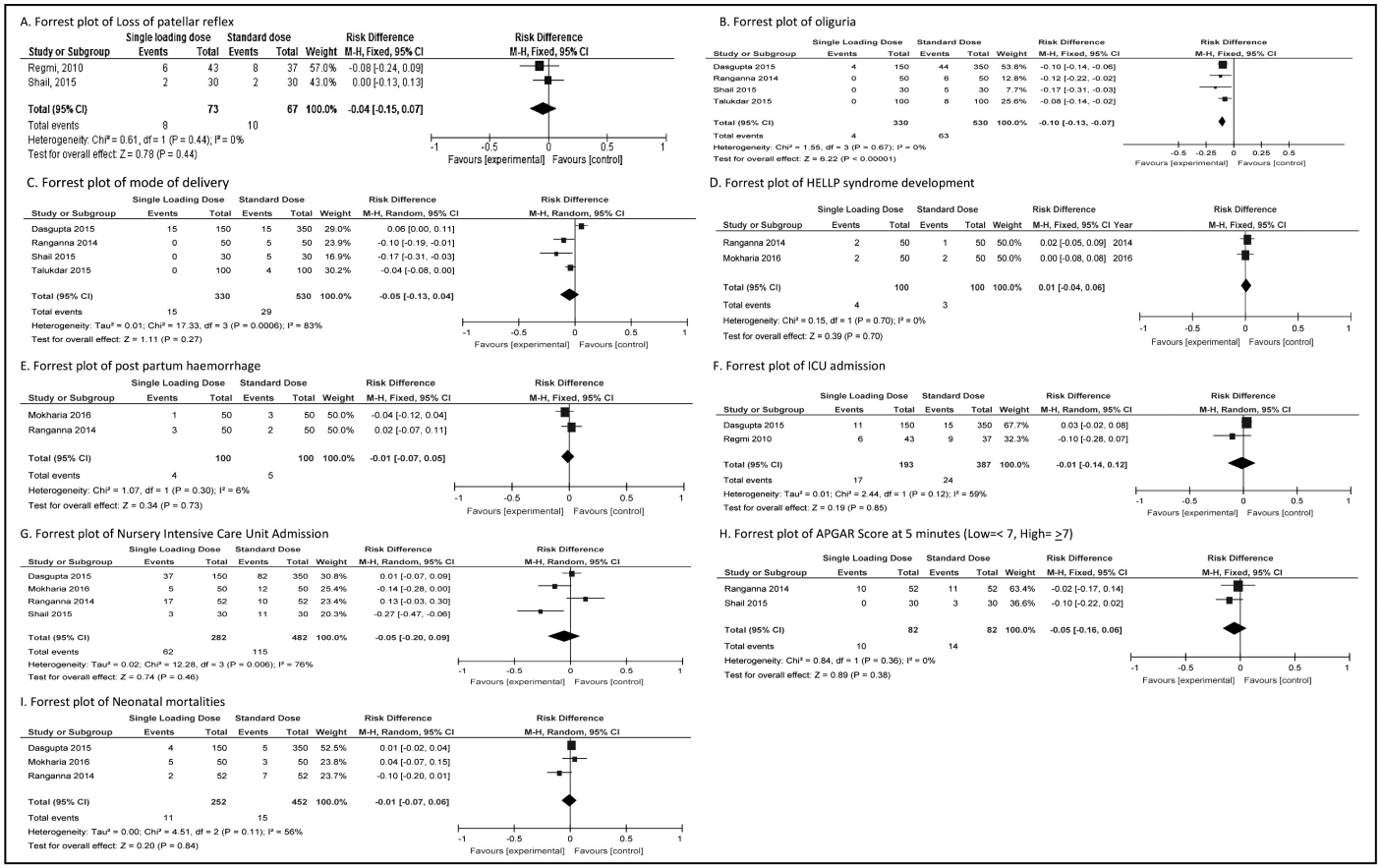

Figure 5. Forrest plots of secondary outcome: *A-Loss of patellar reflex, B-Oliguria, C-Mode of Delivery, D-HELLP Syndrome Development, E-Postpartum haemorrhage development, F-ICU admission, G-NICU admission, H-APGAR Score at 5 mins, I-Neonatal mortalities*

The loading-dose only concept was suggested by Boyd and Browse[22] and was entertained since some patients were not given maintenance doses and did not have further convulsions. However, this regimen was based mainly on western women and was far more than their Filipina counterparts.

Phuapradit et al. found that mean serum magnesium levels were significantly lower in women having >70kg than those with <70kg[23] which is quite similar in Filipinas. Brandt and Chesley explained that $MgSO_4$ is distributed throughout the body especially in skeletal tissues and only an ample amount is left in the extra cellular fluid. Since lighter patients have lower total body volume, serum drug concentration is higher during maintenance doses.[24]

As the primary goal of this study, our results showed that single loading dose of MgSO4 was enough to prevent primary and recurrent convulsions in preeclamptic and eclamptic women and is comparable to standard 24-hour maintenance therapy. Similar studies revealed same results.[16,26,27] Developing countries may benefit from this loading dose regimen since population and standard of living is comparable to the Philippines and was carried out in low resource countries like Pakistan,[16] Bangladesh,[28] Nepal[29] and Nigeria.[11] Alterations of dosing and frequency were studied and Anjum et al showed no convulsions were recorded after either $MgSO_4$ infusion between 12 or 24 hours after delivery.[30] Darngawn et al. showed that in severe preeclampsia, even a shortened (6-hour) $MgSO_4$ regime was as effective as 24-hour with significant benefits such as cost and morbidity.[13] This was further exemplified in an RCT done India where a 4g loading dose followed by a 2g $MgSO_4$ given every 3 hours for 24 hours was still effective.[31] A quasi-randomized case control study also failed to show significant difference between the 2 regimens.[10] Other low dose approach showed treatment cost-effectiveness was also reduced by more than 50%.[32]

Regmi et al, found that recurrent convulsions appeared in 4.6% in loading dose only group however, a case of meningoencephalitis was later diagnosed probably owing to the incident.[29] Sibai and Ramanthan found that 10.0% of eclamptics experienced further convulsion but since that study evaluated western women, less occurrence in our study can be attributed to the lesser body weights of Asian and hence be applied to Filipinas of the same body type.[33]

Regarding $MgSO_4$ toxicity, results showed strong statistical significance in decreased patellar reflex in favor of loading dose only group and non-significant results in oliguria. However, Shail only showed comparable results on both groups.[34]

The rest of the maternal outcomes such as the occurrence of cesarean section, progression to HELLP syndrome, post-partum hemorrhage and MICU admissions showed similar results. All neonatal outcomes comparing loading versus standard $MgSO_4$ therapy showed to be non-significant. However among the 3 parameters stated, NICU admission had high heterogeneity. This may be attributed to the differences in definition of NICU admissions of the included studies. Ranggana stated that between the two groups, loading dose group had better perinatal outcome than the control group however only the incidence of neonatal death was statistically significant.[35] Other concerns regarding neonatal outcome was decreased time-gap to contact newborn after delivery improving the likelihood of establishing breastfeeding.[36]

Aside from having the objectives met, it is suitable in developing countries like the Philippines where average body weight is low, monitoring is difficult and resource-availability is limited. This was found to be associated with significant patient satisfaction in terms of quicker return to postnatal wards and shorter hospital stay.[37]

CONCLUSION

Administering single loading dose of $MgSO_4$ is comparable to the standard 24-hour therapy in preventing seizures and recurrence of preeclamptic and eclamptic patients. Maternal and neonatal outcomes of both protocol had no significant difference with some advantages of lesser maternal $MgSO_4$ toxicity issues. This study encourages doctors especially in developing countries such as the Philippines to at least give the loading dose prior to transfer to a higher and more capable medical institution in preventing serious morbidities and mortalities.

LIMITATIONS

This study only includes randomized controlled trials comparing single loading dose of $MgSO_4$ to standard 24 hour regime in women with pre-eclampsia and eclampsia at any time of the pregnancy. The trimesters as to when the patients were given were not given emphasis. Those who received previous doses of MgSO4 or anticonvulsants prior to treatment were excluded as well as those patients with co-morbidities. Also, cost-effectiveness was not measured and compared.

RECOMMENDATIONS

Future enthusiasts may dwell in the following areas not covered in this study:

1. Over-all medical cost-effectiveness such as medications, materials used and hospital charges including room fees or specialist fees per day.
2. Subdivision of trimesters as to when the patients were diagnosed giving a detailed neonatal outcome result.
3. A correlation study since several literatures suggest a lower $MgSO_4$ concentration in lower body mass index of Asian women including Filipinas.

The researchers hope that this study will help in building an updated national protocol of pregnant Filipina patients with preeclampsia and eclampsia.

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