

Role of Magnesium Sulphate in Ischaemic Stroke

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Objective: To evaluate the role of magnesium sulphate in patients presenting with ischaemic stroke. **Methods:** This experimental type of interventional study was carried out at Mayo Hospital, Lahore. Within 24 hours of onset of clinically diagnosed stroke, which was later confirmed by CT scan, patients were randomized to receive either magnesium sulphate (16mmol IV over 15 minutes and 65mmol over 24 hours) or placebo. Their disability was measured by Barthel score at presentation and outcome measured after three months by death and disability and the results were compared between the two groups. Those patients who had a Barthel score of ≥ 12 at three months were considered independent and those with a score of < 12 were considered disabled. The results were analyzed by SPSS. **Results:** Fifty patients were recruited in the study. 25 patients were randomized to receive $MgSO_4$ and 25 received placebo. The Barthel score improved from 5.1 ± 3.3 at presentation to 13.5 ± 3.4 after three months in all the patients so there was improvement whether $MgSO_4$ was given or not. Patients who were randomized to receive $MgSO_4$ had a lower Barthel score of 4.2 ± 2.9 as compared to controls 5.9 ± 3.5 , but after three months they improved more than the controls gaining a score of 15.7 ± 1.9 versus 11.3 ± 3.2 ($p=0.000$). The mortality rate was not statistically different in the two groups. 88% patients had a Barthel score of > 12 at three months in the $MgSO_4$ and 30% in the control/placebo group. Combined death and disability was 8% in $MgSO_4$ group and 60% in the control group. Moreover $MgSO_4$ was well tolerated. **Conclusion:** Magnesium sulphate therapy was safe in patients presenting with ischaemic stroke irrespective of the site of infarct. It improves prognosis regarding Barthel score at three months as well as the difference in the Barthel score at presentation and at three months. A greater percentage of magnesium treated patients led independent lives after three months.

Key words: Magnesium sulphate, ischaemic stroke

Stroke is one of the leading causes of death and disability in the world. The management of stroke is quite expensive; its costs exceed 51 billion dollars annually in the US. The characteristic sudden onset and rapid tissue damage make stroke particularly challenging to treat. The most promising therapy for acute ischaemic stroke is the use of thrombolytic agent, intravenous t-PA which is FDA approved. Many neuroprotective agents are also available but there is extensive clinical experience with magnesium which acts at the ischaemic penumbra, a potentially salvageable area around an infarct. Once this penumbra is protected, the infarct size and therefore disability can be limited. Ischaemia causes impaired energy production and excessive release of glutamate, that excites the NMDA receptors which cause influx of sodium chloride, water and calcium. This results in neuronal damage. Magnesium is a NMDA receptor blocker. It also abolishes cerebrovasospasm, is a glutamate release inhibitor and calcium channel antagonist. Moreover it is safe and tolerable.

Material & Methods

Study design: This is an experimental type of interventional study.

Subjects: Fifty patients presenting with clinically diagnosed stroke within 24 hours were randomized to receive placebo or intravenous magnesium sulphate. Twenty-five patients received magnesium sulphate and twenty-five received placebo, which was in the form of normal saline infusion.

On receiving the patients, complete history was taken, risk factors identified and general physical

examination along with neurological examination was performed. Disability was assessed by Barthel score as shown in Table I.

Barthel Index/Score

This score assesses the activities of daily life and scores are allocated according to the level of difficulty in performance of these activities. The maximum score is 20. Patients scoring ≥ 12 will be considered independent and those scoring < 12 will be considered disabled.

Inclusion Criteria: Patients with acute ischaemic stroke. A CT Scan was performed to rule out haemorrhage.

Exclusion Criteria

1. Haemorrhagic stroke.
2. Hypotension.
3. Renal failure.
4. Hepatic failure.
5. Any serious concurrent condition.
6. TIA

The procedure: Patients receiving magnesium sulphate received it in a dose of 16 mmol infusion over 15 minutes and then 65 mmol infusion over the next 24 hours, under cardiovascular monitoring. Magnesium sulphate (Spasmeq) injection is available in strength of 4.9mmol.

Three and quarter ampoules were used to make a strength of 15 mmol and diluted in injection 0.9% normal saline in 100 cc microburette and infused intravenously rapidly over 15 minutes. The next dose was prepared by adding four and half ampoules of injection Spasmeq diluted in injection 0.9% normal saline and run intravenously at 12-13 microdrops per minute over 8

hours. Three such infusions delivered 65 mmol of MgSO₄ in 24 hours.

Patients receiving placebo were given normal saline infusion over 24 hours.

Duration of follow-up: Patients were followed up to three months.

End Point of Study

1. Death of the patient
2. Disability as measured by Barthel score

Statistics: Statistical analysis was made using SPSS. Efficacy of MgSO₄ was assessed by comparing outcome of study group with control group using Paired-Sample T test.

Table I: The Barthel Index/Score

Item	Categories
1 Bowels	0 = incontinent 1 = occasional accident 2 = continent
2 Bladder	0 = incontinent/ catheterized, unable to manage 1 = occasional accident 2 = continent
3 Grooming	0 = needs help 1 = independent for face/ hair/ teeth/ shaving
4 Toilet use	0 = dependent 1 = needs some help 2 = independent
5 Feeding	0 = dependent 1 = needs help e.g. cutting, spreading butter 2 = independent in all actions
6 Transfer (bed- chair)	0 = unable 1 = major help, can sit 2 = minor help (verbal or physical) 3 = independent
7 Walking	0 = unable 1 = independent in wheelchair 2 = walk with help of person (verbal/ physical) 3 = independent (may use aid)
8 Dressing	0 = dependent 1 = needs help but does half 2 = independent (including buttons, zips, laces)
9 Stairs	0 = unable 1 = needs help (verbal/ physical) 2 = independent
10 Bathing	0 = dependent 1 = independent

Results:

The baseline characteristics of all the patients are shown in Table 16. Patients presented had an age range of 20-80 years with an average of 56 years. 33 (66%) patients presented with right-sided weakness of the body and 17 (34%) patients presented with left- sided weakness of the body. Changes in systolic and diastolic BP and pulse rate in Mg group did not differ from those in the control group. Table II shows the Barthel score at presentation, after three months and the improvement in the score.

The Barthel score improved from 5.5 ± 3.3 at presentation to 13.5 ± 3.4 after three months. So there was an improvement whether or not MgSO₄ was given. Barthel score at presentation in patients who were assigned to

MgSO₄ was 4.2±2.9 as compared to those who were not given MgSO₄ with a Barthel score of 5.9 ± 3.5. Despite this fact, the absolute value of Barthel score at three months was more 15.7 ± 1.9 versus 11.3 ± 3.2 as compared to the control group (p=0.000). The overall improvement in Barthel score was much better in MgSO₄ group as compared to the control group, 11.3±2.3 versus 4.9±1.2 respectively.

2(8%) patients died in the MgSO₄ group and 3(12%) died in the control group, but this is not statistically significant. Fewer magnesium treated patients were dead and none disabled at three months (n=2, 8%) compared with the control group, where patients dead or disabled (Barthel score <12) were n= 15, 60%. Patients with a Barthel score of >12 at three months were 88% in magnesium treated group and 30% in the control group.

Moreover MgSO₄ had been safe and well tolerated by all the patients with no side effects reported.

Paired-Sample T test was applied to test the significance of the absolute Barthel score at three months and the improvement obtained in the two groups and it showed that the results are statistically significant.

Table II:Barthel score at presentation,at 3months & improvement in score

Parameters	Barthel score at presentation	Barthel score after 3 months	Improvement in score
MgSO ₄ Group	4.2 ± 2.9	1.5±1.9 (p=0.000)	11.3 ± 2.2 (p = 0.000)
Control Group	5.9 ± 3.5	11.3±3.2	1.10± 1.2

Discussion:

The objective of the study was to evaluate the effect of MgSO₄ in ischaemic stroke. Magnesium has been shown to be neuroprotective in many preclinical models of ischaemic brain injury. This has been proven in standard animal focal cerebral ischaemic models. Marinov and his associates injected MgSO₄ intraarterially before induction of reversible ischaemia during cerebrovascular surgery in rats and it reduced the size of infarct as compared to controls². Reduction in infarct size by magnesium was also observed in rats in a study by Izumi and associates in which middle cerebral artery was occluded³.

Muir has also observed these benefits in humans⁴. In a study by Lampl and his colleagues, it was observed that lower the serum and CSF magnesium levels, the greater the neurological deficit⁵ and therefore this proves that higher the magnesium levels, the lesser the neurological deficit. A meta-analysis of four small clinical trials (n=170) of intravenous magnesium in stroke favours its treatment. The neuroprotective effects of magnesium sulphate were therefore studied in our local population.

Patients presenting to the emergency department with clinically diagnosed ischaemic stroke, within 24 hours of onset of symptoms, in the form of weakness of either half of the body were selected for the study and randomized to receive placebo or MgSO₄. In a study by Muir and Lees,

patients presenting within 24 hours of onset of clinically diagnosed stroke were chosen.¹ In an ongoing large multicentre trial, the IMAGES study group, patients presenting within 12 hours of stroke with limb weakness are eligible⁶.

MgSO₄ was infused at a dose of 16mmol over 15 minutes followed by 65mmol over 24 hours with no side effects. This is the same dose that has been chosen for IMAGES study group and has been proven to be effective in the study by Muir and Lees. They demonstrated that 16mmol-loading dose achieved target serum concentration most rapidly and the level was maintained for at least 24 hours. This dose was safe and tolerable with no major haemodynamic effects. In a previous study done by the same workers Muir & Lees, the initial loading dose was 8mmol over 15 minutes with the same maintenance dose, but with this dose the desired serum concentrations were not achieved⁷. Another clinical trial of MgSO₄ in acute stroke conducted by Wester and his colleagues showed that there was no evidence of undesirable neurological or cardiovascular effects⁷. The largest demonstration of safety and tolerability was ISIS-4⁸, in which 29011 patients with acute MI received MgSO₄. Magnesium acts as a vasodilator and has previously been found to lower systemic BP. Reduction of systemic BP in the acute phase after ischaemic stroke is detrimental to survival, as was evident in Intravenous West European Stroke Trial (INWEST), in which dose dependent worsening of neurological outcome correlated with the degree of lowering of diastolic BP. In our study there was no difference in BP between magnesium and placebo-treated groups. No side effects were reported with magnesium infusion. The LIMIT-2 trial used 8mmol loading dose and 65mmol maintenance and reported transient flushing and warmth in association with loading dose.

The primary outcome was death and disability as measured by Barthel score at three months. This is the same as in the IMAGES study group. The mortality rate was same in the MgSO₄ group and the controls. The Barthel score at presentation improved in all the patients after three months and so there was improvement whether or not MgSO₄ was given. Barthel score of patients who received MgSO₄ had a lower score of 4.2±2.9 than those of controls with a score of 5.9±3.5 at presentation. This means that the first group was at some disadvantage. Despite this the MgSO₄ group patients improved farther more at three month with a score of 15.7±1.9 than controls with a score of 11.3±3.2. Patients with a score of ≥12 are independent and <12 are disabled. So all the patients in the MgSO₄ group were independent after 3 months, except those who have expired, but not all in the control group. The difference in the mean Barthel scores in the two groups was not compared in the study done by Muir and Lees. In our study, patients dead or disabled in MgSO₄ group were 8% and in the control group 60%. The patients dead or disabled at three months in the MgSO₄ group was

30% and in the control group was 40% in Muir and Lees study. Therefore the results were equivocal in Muir and Lees study, but favour MgSO₄ therapy according to our study. Their mortality was 20% in MgSO₄ group and 23% in control group, which is more as compared to our study. The patients who led an independent life after three months (Barthel score >12) were 70% in magnesium group and 60% in the control group in Muir and Lees study, whereas the respective scores were 88% and 32% in our study. The increase score in the magnesium treated group in our study might be explained due to the higher loading dose of magnesium. The multicentre, randomized placebo controlled IMAGES study is still in progress and its results will soon be available. No local study has yet been conducted so that the above results can be compared with. The above results support the hypothesis that MgSO₄ is neuroprotective.

The observed risk factors in the basic characteristics of the study population are comparable to the study done by Ather Javed and his colleagues¹⁷. The two groups in the study had almost similar characteristics.

Conclusion:

1. Magnesium sulphate therapy is safe in patients with ischaemic stroke irrespective of site and size.
2. It improves prognosis regarding absolute Barthel score at three months as well as the difference between presentation and three months Barthel score. On the basis of above observation it is suggested that MgSO₄ may be given to all patients suffering from ischaemic stroke. However, a larger study is required to confirm the findings.

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