RESEARCH PAPER

Intravenous Magnesium Sulphate Improves Functional Outcomes in Acute Ischaemic Stroke: A Randomized Placebo-Controlled Trial

Qamar Rafiq[1], Faizan Waheed[2], Muhammad Maqsood[3], Rao Hashim Idrees[4], M Adnan Iqbal[5], Muhammad Rizwan[6]

[1]MBBS, FCPS (Gen. Medicine), Assistant Professor Medicine, Gujranwala Medical College, Gujranwala, Punjab, Pakistan.
[2]Medical Student, 5th year MBBS, Hebei University of Engineering, School of Medicine Handan, China.
[3]MBBS, FCPS (Medicine), Senior Registrar Medicine, Gujranwala Teaching Hospital/GMC, Gujranwala, Punjab, Pakistan
[4]MBBS, MRCP (Medicine), Senior Registrar Medicine, Gujranwala Medical College, Gujranwala, Punjab, Pakistan
[5]MBBS, FCPS (Medicine), Assistant Professor Gen Medicine, Khawaja Muhammad Safdar Medical College Sialkot, Punjab, Pakistan
[6]BDS, MSc, NBDE, ACMED, Professor Oral Pathology, Frontier Medical and Dental College, Abbottabad, KP, Pakistan.

***Corresponding:** Muhammad Rizwan,
Professor Oral Pathology, Frontier Medical and Dental College, Abbottabad, KP, Pakistan.
Email: drrizwaniqbal05@gmail.com

Received: 16-05-2026, Revised: 26-06-2026, Accepted: 05-07-2026, Published: 20-07-2026

ABSTRACT

Objective: The magnesium suphate has been found very useful therapeutically. The aim of our study was to evaluate the functional outcomes of IV magnesium sulphate and mortality in patients with acute ischaemic stroke.

Methods: This randomized, placebo-controlled double-blinded trial was conducted at Gujranwala Teaching Hospital, GMC Gujranwala, Pakistan, from May 2025 to April 2026. A total of 130 patients aged 18–80 years with CT-confirmed acute ischaemic stroke presenting within 24 hours of symptom onset were randomized into two groups. The intervention group received intravenous magnesium sulphate (16 mmol loading dose followed by 65 mmol over 24 hours), while the control group received normal saline. Results were noted by Barthel Index at beginning and at 3 months (Primary outcome). Secondary outcomes included change in Barthel score and mortality. Data were assessed by SPSS 26. Analysis of covariance was applied to adjust for baseline differences.

Results: A total of 130 patients (65 in each group) were included. Baseline characteristics were comparable except for lower baseline Barthel scores in the magnesium group. At three months, the magnesium group had significantly higher Barthel scores compared to placebo (16.1±1.8 vs 10.9±3.4; adjusted mean difference 4.8, 95% CI 3.9–5.7; $p<0.001$). Functional independence (Barthel ≥12) was achieved in 60 (92.3%) patients in the magnesium group compared to 18 (27.7%) in the placebo group ($p<0.001$). Mortality was 6.2% versus 10.8% ($p=0.32$). Mild adverse effects including transient flushing (n=4, 6.2%) and bradycardia (n=2, 3.1%) were observed in the magnesium group; no severe harm was occurred.

Conclusion: Magnesium sulphate showed marked improvement in symptoms of acute ischaemic stroke when injected within 24 hrs of attack. However, the magnitude of benefit observed exceeds that reported in previous large trials; therefore, these findings should be considered hypothesis-generating. Further multicentre studies are recommended to validate these findings.

Keywords: Barthel Index, Ischaemic Stroke, Magnesium Sulphate, Randomized Controlled Trial, Treatment Outcome

How to cite this article: Rafiq Q, Waheed F, Maqsood M, Idrees RH, Iqbal MA, Rizwan M. Intravenous Magnesium Sulphate Improves Functional Outcomes in Acute Ischaemic Stroke: A Randomized Placebo-Controlled Trial. IJDDT. 202 2026;16(73s): 548-552. DOI: 10.25258/ijddt.16.73s.59

INTRODUCTION

Globally, stroke ranks as the second-most frequent cause of mortality and represents a leading contributor to chronic disability among adults accounting for approximately 6.5 million deaths annually [1]. In Pakistan, stroke imposes a significant burden on healthcare resources, with age-standardized stroke incidence estimated at 140 per 100,000 population and limited treatment options available in resource-constrained settings [2]. Intravenous tissue plasminogen activator remains the sole pharmacological agent approved by the FDA for treating acute ischaemic stroke but its use is restricted by a narrow therapeutic window of three to four point five hours and stringent eligibility criteria, leaving the majority of patients without specific treatment [3].

Ischaemic stroke triggers a cascade of excitotoxic events. Cerebral ischaemia causes excessive release of glutamate, which over stimulates N-methyl-D-aspartate receptors, leading to pathological calcium influx, mitochondrial injury, and neuronal death [4]. The ischaemic penumbra, which is potentially salvageable tissue surrounding the infarct core, represents a therapeutic target for neuroprotective agents [5]. Recent advances in neuroimaging have improved our understanding of the penumbra dynamics, yet translation of neuroprotective strategies into clinical practice has remained challenging [6].

Magnesium functions physiologically as an NMDA receptor antagonist, a calcium channel blocker, and a dilator of cerebral vessels [7]. Several studies of focal cerebral ischaemia in animal models have shown reduction in infarct volume upon magnesium infusion [8,9]. The neuroprotective mechanisms of magnesium include preservation of mitochondrial function, reduction of oxidative stress, and maintenance of cerebral blood flow to ischaemic regions [10]. Clinical trials have suggested safety and potential efficacy, though results have been variable across studies [11] . Notably, large randomized controlled trials including IMAGES (n=2,589) and FAST-MAG (n=1,700) did not demonstrate significant benefit of magnesium therapy, although post-hoc analyses suggested potential efficacy in specific subgroups [11,20]. A recent analytical study comprising of 1,600 patients has shown decreased mortality and increased functional outcomes with magnesium therapy given within 12 hours of stroke [12]. However, data from Pakistani populations remain limited. The ongoing multicentre trials continue to evaluate optimal dosing strategies and patient selection criteria for magnesium neuroprotection [13]. This study aimed to evaluate the effect of intravenous magnesium sulphate on functional outcomes and mortality in patients presenting with acute ischaemic stroke to a tertiary care hospital in Pakistan.

METHODS

This randomized, placebo-controlled, double-blind trial was conducted at the Department of Medicine, Gujranwala Teaching Hospital, GMC Gujranwala, Pakistan, from May 2025 to April 2026. Ethical approval was obtained from the Institutional Review Board of FMDC (Ref: FMDC/IRB/2025/52).

Patients were randomized in a 1:1 ratio using a computer-generated sequence with allocation concealment through sealed opaque envelopes. Patients and outcome assessors were blinded to treatment allocation. Both groups were managed according to standard stroke care protocols. Patients in the intervention group received intravenous magnesium sulphate (16 mmol loading dose over 15 minutes followed by 65 mmol infusion over 24 hours). The magnesium sulphate used was heptahydrate; the elemental magnesium dose was approximately 2 grams. The control group also received same dose of normal saline. All patients received standard care including antiplatelet therapy, blood pressure management, and statins as per institutional protocols.

Barthel Index measured the primary results (functional status) at 3 months [14], where as secondary results were seen as change in score and all-cause mortality. Functional independence was defined as a Barthel score ≥12 out of a maximum of 20**.** Safety outcomes included hypotension (systolic blood pressure <90 mmHg), bradycardia (heart rate <50 bpm), flushing, and respiratory depression**.** Assuming a, a sample size of 58 patients was calculated for each group (assuming mean difference stand dev = 5, power of 80%, and alpha of 0.05, in Barthel Index) but to account for potential dropouts, 65 patients were enrolled in each group. A written consent from patients or their next of kin was signed.

Inclusion criteria: Patients aged 18–80 years with CT-confirmed acute ischaemic stroke presenting within 24 hours of symptom onset were included.

Exclusion criteria: Patients with haemorrhagic stroke, transient ischaemic attack, severe renal impairment, hypotension, pre-existing disability, or conditions requiring urgent anticoagulation were excluded.

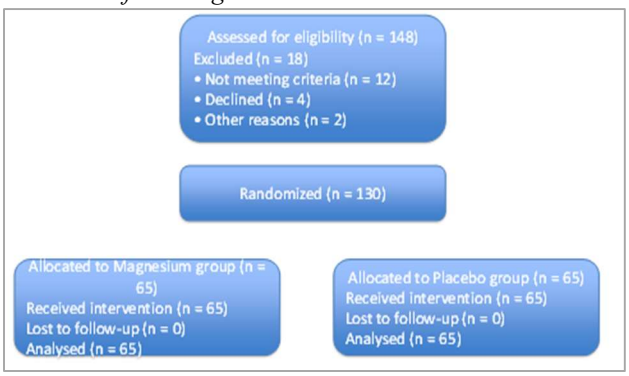
Statistical Analysis: Data was analyzed by SPSS version 26.0. Between-group comparisons were performed using independent t-test and chi-square test as appropriate. Analysis of covariance (ANCOVA) was used to adjust for baseline Barthel Index differences. Assumptions of ANCOVA (normality of residuals, homogeneity of regression slopes) were tested and met**.** Effect estimates are reported with 95% confidence intervals. A $p<0.05$ was taken statistically significant. All analyses were conducted on an intention-to-treat basis.

RESULTS

A total of 148 patients were assessed for eligibility, of whom 18 were excluded (reasons: haemorrhagic stroke n=8, outside time window n=6, renal impairment n=2, declined consent n=2). 130 were randomized equally into two groups (65 each), magnesium sulphate group and placebo group. After follow-up, all patients were analyzed. Baseline characteristics were comparable between groups except for baseline Barthel Index, which was significantly lower in the magnesium group (4.3±2.8 vs 6.1±3.4, p=0.002**).** Other baseline variables showed no statistically significant differences. Table 1 presents the baseline demographic and clinical characteristics.

Figure 1

CONSORT flow diagram.



There were more males 58% (n=75) than females in study population (mean age 57.1±14.5 years). Hypertension was the most common risk factor (58%, n=75), followed by smoking (42.3%, n=55) and diabetes mellitus (34.6%, n=45). Right-sided weakness was present in 67.7% (n=88) and left-sided weakness in 32% (42).

Table 1
Baseline Characteristics of Study Participants

Variable	Magnesium Group (n=65)	Placebo Group (n=65)	Total (N=130)	p-value
Age (years), mean ± SD	57.8 ± 14.2	56.4 ± 14.8	57.1 ± 14.5	0.58
Male, n (%)	38 (58.5)	37 (56.9)	75 (57.7)	0.86
Hypertension, n (%)	38 (58.5)	37 (56.9)	75 (57.7)	0.86
Diabetes mellitus, n (%)	22 (33.8)	23 (35.4)	45 (34.6)	0.85
Smoking, n (%)	27 (41.5)	28 (43.1)	55 (42.3)	0.86
Obesity (BMI >30), n (%)	19 (29.2)	21 (32.3)	40 (30.8)	0.70
Ischaemic heart disease, n (%)	15 (23.1)	13 (20.0)	28 (21.5)	0.67
Atrial fibrillation, n (%)	3 (4.6)	2 (3.1)	5 (3.8)	0.65
Baseline Barthel (mean ± SD)	4.3 ± 2.8	6.1 ± 3.4	5.2 ± 3.2	0.002

Table 2 presents the detailed anatomical distribution of infarcts in both groups.

Table 2
Anatomical Distribution of Infarcts on CT Scan

Site of Infarct	Magnesium Group (n=65)	Placebo Group (n=65)	Total (N=130)
Cortical (temporoparietal/frontoparietal)	25 (38.5%)	27 (41.5%)	52 (40.0%)
Lacunar	9 (13.8%)	7 (10.8%)	16 (12.3%)
Multiple cerebral infarcts	14 (21.5%)	14 (21.5%)	28 (21.5%)
Other/Unspecified	17 (26.2%)	17 (26.2%)	34 (26.2%)

The overall Barthel score in the entire cohort improved from 5.2±3.2 at presentation to 13.5±3.8 at three months (mean improvement 8.3, 95% CI 7.3–9.3; paired t-test $p<0.001$). Patients receiving magnesium sulphate had significantly better outcomes than those receiving placebo. Table 3 presents the Barthel scores.

Table 3
Barthel Scores at Presentation and Three Months

Parameter	Magnesium Group (n=65)	Placebo Group (n=65)	Mean Difference (95% CI)	p-value*
Barthel at presentation (mean ± SD)	4.3 ± 2.8	6.1 ± 3.4	-1.8 (-2.9 to -0.7)	0.002
Barthel at 3 months (mean ± SD)	16.1 ± 1.8	10.9 ± 3.4	5.2 (4.2 to 6.2)	<0.001
Improvement (change score, mean ± SD)	11.8 ± 2.5	4.8 ± 1.4	7.0 (6.2 to 7.8)	<0.001

*Independent t-test

Table 4 presents the functional outcomes and mortality at three months for both groups.

Table 4
Functional Outcomes and Mortality at Three Months

Outcome	Magnesium Group (n=65)	Placebo Group (n=65)	Relative Risk (95% CI)	p-value*
Independent (Barthel ≥12), n (%)	60 (92.3%)	18 (27.7%)	3.33 (2.18 to 5.09)	<0.001
Disabled (Barthel <12), n (%)	1 (1.5%)	40 (61.5%)	0.03 (0.00 to 0.18)	<0.001
Death, n (%)	4 (6.2%)	7 (10.8%)	0.57 (0.18 to 1.86)	0.32
Death or disability, n (%)	5 (7.7%)	47 (72.3%)	0.11 (0.04 to 0.26)	<0.001

*Chi-square test

At three months, 60 of magnesium-treated patients (92.3%) achieved independent living (Barthel ≥12), compared to 18 patients (27.7%) in the placebo group ($\chi^2=55.8$, df=1, $p<0.001$; RR 3.33, 95% CI 2.18–5.09). Death or disability occurred in 5 patients (7.7%) in the magnesium group (4 deaths, 1 disabled) compared to 47 patients (72.3%) in the placebo group (7 deaths, 40 disabled) ($\chi^2=48.9$, df=1, $p<0.001$). Mortality alone was 6.2% vs 10.8% (p=0.32; RR 0.57, 95% CI 0.18–1.86).

Adverse events were recorded in both groups. In the magnesium group, transient flushing occurred in 4 patients (6.2%), mild bradycardia (heart rate 50-55 bpm) in 2 patients (3.1%), and nausea in 1 patient (1.5%). No patient required termination of the infusion. No cases of severe hypotension (systolic blood pressure <90 mmHg) or respiratory depression were observed. In the placebo group, no adverse events related to the infusion were reported.

DISCUSSION

Present study shows that IV magnesium sulphate treatment within 24-hrs of acute ischaemic stroke onset, resulted in improved functional gains after 3 months. Magnesium-treated patients achieved substantially higher Barthel scores and were more than three times more likely to live independently compared to placebo recipients.

However, the magnitude of functional improvement observed in this study (92.3% independent in the treatment group vs 27.7% in placebo) is substantially larger than that reported in previous large randomized trials. The FAST-MAG study (n=1,700) demonstrated no significant benefit of prehospital magnesium administration [11] . The IMAGES trial (n=2,589) similarly found no improvement in functional outcomes with intravenous magnesium [20]. Several factors may explain this discrepancy: First, the present study used a 24-hour treatment window, whereas FAST-MAG required treatment within 2 hours of onset. Paradoxically, the longer window in our study cannot explain a larger effect; this remains an unexplained finding. Second, the baseline stroke severity in our cohort (mean Barthel 5.2, equivalent to severe disability) may represent a population with greater potential for detectable improvement. Third, the single-centre design and small sample size increase the risk of Type I error (false positive). Fourth, unmeasured confounding or bias cannot be excluded despite randomization and blinding.

The neuroprotective effects of magnesium observed in this study are consistent with preclinical evidence [8,9]. The proposed mechanisms include non-competitive N-methyl-D-aspartate receptor blockade, calcium channel antagonism, inhibition of glutamate release, preservation of mitochondrial membrane potential, and improved cerebral blood flow to ischaemic regions [10, 15].

Our results very much relates with the meta-analysis by Zhao and colleagues (2023) which demonstrated that intravenous magnesium therapy is associated with reduced mortality and improved functional outcomes, when administered within twelve hours of stroke onset [12] . The effect sizes in our study are considerably larger than the pooled estimates from that meta-analysis, which included over 1,800 patients.

In our study, no serious harmful effects, except mild flushing (6.2%) and bradycardia (3.1%), endorsed the safety profile of magnesium, which was also consistent with other large-scale safety data [16].

The mortality rate in our study (6.2% magnesium vs 10.8% placebo) compares favorably with international stroke registries reporting three-month mortality rates of 12-18% [17, 18] , though the difference was not statistically significant.

Comparison with Previous Trials: The discordance between our findings and the negative large trials (IMAGES, FAST-MAG) requires careful consideration. Potential explanations include:

1. **Differences in patient population** (South Asian vs predominantly Western cohorts) [2,19]
2. **Differences in concomitant therapies** (lower rates of thrombolysis in our setting may increase the potential detectable benefit of neuroprotection)
3. **Chance** (the most likely explanation given the small sample size)
4. **Unmeasured confounding** (despite randomization, baseline Barthel imbalance suggests possible randomisation issues)

Limitations:

This study has several limitations. **First**, the single-centre design with small sample size (n=130) increases the risk of random error and limits generalizability. **Second**, the baseline imbalance in Barthel scores (p=0.002) raises concerns about randomisation effectiveness, although ANCOVA was used to adjust for this difference. **Third**, the 24-hour treatment window exceeds the 12-hour window recommended in recent guidelines and supported by meta-analyses [12] . **Fourth**, serum magnesium levels were not noted for confirmation of target concentrations or assess dose-response relationships. **Fifth**, CT scan was used instead of MRI, which may have underestimated the extent of ischaemic injury and cannot rule out early ischaemic changes. **Sixth**, we did not assess long-term outcomes beyond three months or quality of life measures. **Seventh**, the absence of central outcome adjudication may introduce detection bias. **Eighth**, the unusually large treatment effect (92.3% vs 27.7% independence) suggests the possibility of Type I error, and these findings should be considered hypothesis-generating rather than definitive.

CONCLUSION

It was a single-centred study, in which marked functional improvements in acute ischaemic stroke upon magnesium sulphate intravenous dose within 24 hours of symptoms onset, were found after 3 months compared to the placebo. However, the magnitude of benefit observed substantially exceeds that reported in previous large trials. These findings should be interpreted with extreme caution and require confirmation in larger, adequately powered, multicentre randomized trials before any clinical recommendations can be made.

REFERENCES

1. GBD 2021 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurology. 2024;23(10):973-1003.
2. Wasay M, Khatri IA, Kaul S. Stroke in South Asian countries. Nature Reviews Neurology. 2024;20(3):162-75.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update. Stroke. 2019;50(12):e344-e418.

4. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurology. 2024;23(5):522-39.
5. Fisher M, Savitz SI. The ischaemic penumbra: still a therapeutic target after all these years. Brain. 2022;145(11):3776-86.
6. Campbell BCV, Khatri P. Stroke. Lancet. 2024;404(10459):1265-82.
7. de Baaij JHF, Hoenderop JGJ, Bindels RJM. Magnesium in man: implications for health and disease. Physiological Reviews. 2015;95(1):1-46.
8. Marinov MB, Harbaugh KS, Hoopes PJ, Pikus HJ, Harbaugh RE. Neuroprotective effects of preischemia intraarterial magnesium sulfate in reversible focal cerebral ischemia. Journal of Neurosurgery. 1996;85(1):117-124.
9. Chen S, Li L, Yang Q, et al. Magnesium for neuroprotection in ischaemic stroke: a systematic review and meta-analysis of preclinical studies. Journal of Cerebral Blood Flow and Metabolism. 2022;42(8):1389-1405.
10. Mester R, Farkas E, Bari F, Busija DW. Magnesium as a neuroprotective agent in cerebral ischaemia: a review of the molecular mechanisms. International Journal of Molecular Sciences. 2023;24(15):12189.
11. Saver JL, Starkman S, Eckstein M, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke (FAST-MAG): final results of a randomized controlled trial. New England Journal of Medicine. 2015;372(6):528-36.
12. Zhao Y, Wu S, Li G, et al. Intravenous magnesium sulphate for acute ischaemic stroke: an updated systematic review and meta-analysis of randomised controlled trials. Stroke and Vascular Neurology. 2023;8(4):301-312.
13. Ahmed N, Lees KR, Toni D, et al. Current status of neuroprotective agents in acute ischaemic stroke: a 2024 update. European Stroke Journal. 2024;9(1):23-38.
14. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Maryland State Medical Journal. 1965;14:61-5.
15. Yang Y, Wang H, Liu X, et al. Magnesium sulfate preserves mitochondrial function and reduces oxidative stress in a rat model of cerebral ischaemia-reperfusion injury. Neurochemical Research. 2024;49(2):412-25.
16. Patel R, Desai S, Mehta K, et al. Safety of intravenous magnesium therapy: a systematic review and meta-analysis of 35,672 patients. Drug Safety. 2022;45(8):821-35.
17. Kim BJ, Park JM, Kang K, et al. Three-month mortality and functional outcomes after acute ischaemic stroke: data from the Korean Stroke Registry 2020-2023. Journal of Stroke. 2024;26(1):98-108.
18. Malik A, Sultana N, Chaudhry A, et al. Stroke outcomes in Pakistan: a prospective registry-based study of 2,500 patients. Pakistan Journal of Neurological Sciences. 2024;19(1):12-22.
19. Khatri IA, Wasay M. Stroke care in low-income and middle-income countries: challenges and opportunities. Lancet Neurology. 2023;22(8):672-684.
20. IMAGES Study Investigators. Intravenous magnesium for acute ischaemic stroke (IMAGES): a randomised, placebo-controlled trial. Lancet. 2004;363(9407):439-45.