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Protective Effects of Intravenous Magnesium Sulfate in Stroke Patients Receiving Amiodarone: A Randomized Controlled Trial

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Abstract

Anti-arrhythmic agents, like amiodarone, interfere at different stages of the ischemic stroke. However, amiodarone was accompanied with immunological pulmonary complications and adverse neurological effects. We hypothesize that magnesium sulfate in combination with amiodarone holds promise for stroke treatment. Thirty-six patients with confirmed diagnosis of ischemic stroke and atrial fibrillation who received bolus amiodarone were randomly assigned to magnesium sulfate every 24 h or similar volume of normal saline (as placebo)

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for 5 days. Various severity test scores were used to evaluate the symptoms. Routing biochemistry were also measured at days 1 and 5. Treatment with MgSO4 results in a significant reduction in serum levels of NGAL, Hb, T.Bill, IL-6, IL-8, SNSE, S100B, EGF, PAF, CRP and IgG. Also, MgSO4 treatment significantly improved the RASS, Candida, SOFA, NIHSS and APACHE scores. Moreover, reduction of IL-6, IL-8, SNSE, EGF and APACHE score and increase in RASS score were significantly higher in MgSO4 group compared with placebo. Intravenous administration of MgSO4 in amiodarone-treated stroke patients improved the inflammatory, immunological and neurological indicators and reduced disability in ICU-admitted AIS patients, suggesting that this treatment scheme may prevent amiodarone-induced complications in these patients.

Keywords

Ischemic stroke · Amiodarone · Magnesium sulfate · Ischemia · Severity · Neuroprotection

28.1 Introduction

Ischemic stroke, in which a blood vessel leading to or within the brain is obstructed by a clot and followed by the impaired blood flow, induces neuronal cell death [1], and is the main cause of adult inability and the second leading cause of mortality worldwide [2–5]. Tissue plasminogen activator (tPA), a thrombolytic which targets the thrombus within the blood vessel, is the approved treatment of acute ischemic stroke (AIS) [1, 3, 4]. However, intravenous thrombolysis is not always helpful because most patients with AIS lose the narrow therapeutic time window. Also, recanalization does not always happen, while even if it is achieved, due to the re-obstruction, neurological decay can occur [3]. In this regard, it was reported the recurrent stroke risk is elevated gradually up to 8–12% (within 7 days), 12–15% (within 30 days) and 17–19% (within 90 days) [6].

Development of neuroprotective agents in order to interfere at different stages of the ischemic cascade, to increase the window for recanalization therapy and to save ischemic neurons in the brain from irreversible injury, was as much considerable as thrombolytic treatments [3, 7]. As much as ion channels play a crucial role in the development of ischemic brain injury, amiodarone as a multiple ion channel blocker has neuroprotective effects on the ischemic brain [8]. In addition, due to 50–60% maintenance of sinus rhythm, amiodarone is better than other agents, including dronedarone in treatment of atrial fibrillation (AF) [9], which is associated with significantly high risk of a cerebrovascular accident and elevated morbidity and mortality. Such that, amiodarone treatment was proposed for the prevention of AF after coronary artery bypass grafting [10, 11], while immunological pulmonary complications and adverse neurological effects was reported in amiodarone treated patients [12]. Moreover, it was reported that amiodarone treatment in non-valvular AF patients was accompanied with 1.81-fold increased risk of stroke [13].

Magnesium (Mg), an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, as another neuroprotective agent, acts through several mechanisms such as blood flow elevation to ischemic brain areas, cellular energy metabolism improvement and glutamate dependent necrosis inhibition in the hippocampal neurons [4, 14]. Deficiency of Mg in acute and chronic cerebral ischemia leads to hypoxia and further death in

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cells. Therefore, there is a need of using this neuroprotective and neurotrophic drug in the treatment and prevention of cerebrovascular disease [15]. IMAGES study reported that Mg treatment for acute stroke was potentially safe, cheap, effective [16] and showed no significant adverse side effects [17]. In addition, magnesium sulfate (MgSO4) has shown to be effective for both rate and rhythm control in critically ill patients with new-onset AF and might reduce the need for antiarrhythmic drugs such as amiodarone [18]. It was illustrated that combined postoperative use of MgSO4 with amiodarone was proficient in decreasing the incidence of postoperative AF and MgSO4-mediated reduction was significantly higher than amiodarone alone therapy [19]. Since the combination therapy holds promise for stroke treatment [20], we aimed to investigate the supportive effects of magnesium on the prevention of amiodarone-induced immunological and inflammatory pulmonary complications in patients with stroke.

28.1.1 Materials and Methods

The trial was registered in the Iranian Registration of Clinical Trials (IRCT; ID: IRCT201701011165N16). The trial protocol was approved by the Tehran University of Medical Sciences Ethics Committee (ID: IR.TUMS.VCR.REC.1396.2257).

This randomized double-blind placebo-controlled clinical trial was performed on patients with ischemic stroke admitted to the intensive care unit in the Baqiyatallah Hospital and Sina Hospital (Tehran, Iran). The study was approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences and a written informed consent was obtained from patients prior to inclusion in the study. Thirty-six patients were enrolled in this study. The inclusion criteria were: (1) confirmed stroke by CT Scan, (2) diagnosis of AF, and (3) receiving bolus amiodarone (300 mg bolus followed by 50 mg/hour for 5 consecutive days). Patients with serum creatinine levels greater than 2 mg/dl and those with hypermagnesemia were excluded from the study.

Patients were randomly assigned (using permuted blocks) to either magnesium sulfate or matched placebo (normal saline). In group one, subjects received 15 cc (7.5 g) of magnesium sulfate every 24 h. Similar volume of normal saline was administered to the subjects in the group two.

Post stroke neurologic deficit were evaluated by NIHSS (NIH Stroke Score) during the study. Level of consciousness was monitored by GCS (Glasgow Coma Scale) and RASS (Richmond Agitation Sedation Scale). SOFA (Sequential organ failure assessment) score was used to track multiple organs status such as cardiovascular systems, respiratory systems, nervous systems, liver, coagulation and kidney. APACHE II (Acute Physiology and Chronic Health Evaluation II) scale was used to measure severity of diseased condition based on the acute physiological parameters. Candida score as a bedside scoring system for candida infection in the patients admitted to the ICU was evaluated. Mortality rate during the hospitalization period and up to 3 months' post discharge, hospitalization period, heart rate, blood pressure, respiratory rate, arterial blood gas (ABG) and adverse drug reactions were also recorded daily for each patient during the study.

Laboratory data such as complete blood count with differentials (CBC-diff), pH, lactate, blood urea nitrogen (BUN) and serum levels of creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), neuron-specific enolase (SNSE), S100B, glucose, total bilirubin, sodium, potassium, magnesium and calcium were measured before and after the intervention (days 1 and 5) in both of the study groups. Immunological parameters such as IgM, IgG, interleukin 6 (IL-6), interleukin 8 (IL-8), platelet-activating factor (PAF), plasminogen activator inhibitor-1 (PAI-1), neutrophil gelatinase-associated lipocalin (NGAL) protein, epidermal growth factor (EGF) protein, transforming growth factor β (TGFβ) proteins were measured at day 1 and day 5 using commercial ELISA kits.

28.2 Statistical Analysis

The obtained data were analyzed using the Statistical Package Social Sciences (SPSS) software for Microsoft Windows (SPSS 17.0, SPSS Inc., and Chicago, IL, USA). Within-group (before vs. after) comparisons were made using paired samples t-test and Wilcoxon signed-rank test in case of normal and non-normal distribution of data, respectively. Between-group changes were performed using independent samples t-test and Mann-Whitney U test in case of normal and non-normal distribution data, respectively. $P < 0.05$ were considered as statistically significant.

28.3 Results

28.3.1 Baseline Characteristics

Thirty-six subjects (18 in each group) completed the study with no drop-out and death during the study. There were no significant differences between MgSO4 versus placebo groups in the case of sex, mean ± SD age (65.78 ± 12.13 *vs.* 66.5 ± 12.58) and the percentage of hypertensive (56% *vs.* 33.3%), hyperlipidemic (16.7% *vs.* 11.1%) and diabetic (27.8% *vs.* 22.2%) patients ($P > 0.05$). Baseline values of weight ($P = 0.020$), BMI ($P = 0.015$), IL-6 ($P = 0.043$), IL-8 ($P < 0.001$), SNSE ($P < 0.001$), PAF ($P < 0.001$), PAI ($P < 0.001$), TGF ($P = 0.003$), IgG ($P < 0.001$), PLT ($P < 0.001$), AST ($P = 0.008$) and BUN ($P < 0.001$) showed statistically significant differences between groups. Baseline characteristics of the study population are summarized in Table 28.1.

28.3.2 Effect of MgSO4 on Biochemical Parameters

Using of MgSO4 significantly reduced the serum concentrations of NGAL ($P = 0.034$), Hb ($P = 0.031$), T.Bill ($P = 0.021$); however, the reduction in levels of FBS, WBC, ALT, BUN, Scr, and K and increase in the levels of PLT, AST, NA and lactate were not statistically significant in MgSO4 group ($P > 0.05$). In placebo group, except of PLT concentration ($P = 0.000$) which reduced, the levels of other biochemical parameters were not statistically changed (Table 28.2). Our results showed that the placebo-mediated reduction of PLT level was higher than MgSO4 ($P < 0.001$). Changes in serum levels of other biochemical parameters were not statistically different between groups ($P > 0.05$) (Table 28.3).

28.3.3 Anti-inflammatory Effect of MgSO4 on Brain Function

Using of MgSO4 significantly reduced the serum concentrations of IL-6 ($P < 0.001$), IL-8 ($P < 0.001$), SNSE ($P = 0.011$), S100B ($P = 0.007$), EGF ($P = 0.002$), PAF ($P = 0.005$) and CRP ($P = 0.001$). However, reduction in TGF and PAI levels were not statistically significant in MgSO4 group ($P > 0.05$). In placebo group, except of significant reduction in PAF level ($P = 0.045$), the levels of other inflammatory parameters were not statistically changed ($P > 0.05$) (Table 28.2). Our results demonstrated that MgSO4-mediated reductions of IL-6 ($P = 0.001$), IL-8 ($P < 0.001$), SNSE ($P = 0.016$), S100B ($P = 0.003$) and EGF ($P = 0.037$) levels were significantly higher when compared with placebo, while changes in serum levels of PAF and CRP were not statistically different between groups ($P > 0.05$) (Table 28.3).

28.3.4 Effect of MgSO4 on the Amiodarone-Induced Immunological Indicators

Using of MgSO4 significantly reduced the serum concentrations of IgG ($P = 0.022$), but IgA level ($P > 0.05$) was not altered after MgSO4 treatment. In placebo group the levels of both IgG and IgA were not statistically changed ($P > 0.05$) (Table 28.2). In addition, changes in serum levels of both IgG and IgA were not statistically different between groups ($P > 0.05$) (Table 28.3).

Table 28.1 Baseline comparison between MgSO4 group and placebo group

		MgSO4 (N = 18)	Placebo (N = 18)	P value
Age (y ± SD)		65.78 ± 12.13	66.5 ± 12.58	0.862
Sex	Female	9 (50%)	9 (50%)	1.000
	Male	9 (50%)	9 (50%)	
Hypertension (no. (%))		10 (56%)	6 (33.3%)	0.180
Hyperlipidemia (no. (%))		3 (16.7%)	2 (11.1%)	0.500
Diabetes (no. (%))		5 (27.8%)	4 (22.2%)	0.500
After 3-month mortality (no. (%))		2 (11.1%)	3 (16.7%)	0.500
Weight (kg)		83.78 ± 9.26	76.22 ± 9.32	0.020*
Height (cm)		170.83 ± 9.78	174.61 ± 6.72	0.186
BMI (kg/m^2)		29.07 ± 5.35	25.11 ± 3.81	0.015*
IL-6 (pg/ml)		9.89 ± 2.78	8.33 ± 1.33	0.043*
IL-8 (pg/ml)		25.06 ± 4.39	13 ± 1.53	0.000*
FBS (mg/dl)		188.78 ± 70.06	172.78 ± 93.95	0.566
SNSE (μg/L)		12 ± 2.52	8.39 ± 1.2	0.000*
S100B (pg/ml)		11.83 ± 2.15	12.67 ± 1.37	0.175
PAF (ng/ml)		95.11 ± 24.79	43.39 ± 14.79	0.000*
PAI (ng/ml)		67.39 ± 26.79	12.11 ± 5.5	0.000*
NGAL (ng/ml)		212.39 ± 53.49	207.22 ± 52.83	0.772
EGF (pg/ml)		87.56 ± 36.41	88.56 ± 36.77	0.935
TGF(pg/ml)		10.72 ± 5.68	18.67 ± 8.98	0.003*
IgA (mg/dl)		7.56 ± 1.65	7 ± 1.46	0.292
IgG (mg/dl)		58.06 ± 15.74	28.33 ± 6	0.000*
WBC (cells//μl)		7.78 ± 2.29	7.78 ± 1.44	1.000
PLT (Plt/μl)		158.11 ± 32.3	237.73 ± 60.39	0.000*
Hb (g/L)		10.28 ± 1.49	10.89 ± 1.41	0.214
CRP (mg/L)		10.5 ± 2.07	11.67 ± 2.25	0.114
ALT (mg/dl)		28.78 ± 4.7	26.95 ± 11.02	0.521
AST (mg/dl)		23.61 ± 4.23	19.06 ± 5.33	0.008*
BUN (mg/dl)		23.22 ± 3.39	18 ± 1.46	0.000*
Scr (mg/dl)		1.56 ± 0.57	1.44 ± 0.35	0.486
T.Bill (mg/dl)		1.20 [1–1.7] [a]	1 [1–2][a]	0.772
Na (mEq/L)		141.95 ± 4.67	143.11 ± 12.1	0.705
K (mEq/L)		4.72 ± 0.81	4.37 ± 0.73	0.181
PH		7.31 ± 0.33	7.24 ± 0.41	0.571
Lactate (mg/dl)		1.59 ± 0.61	2.06 ± 0.87	0.072
RASS		(−3) [(−4) – (−2)] [a]	(−3) [(−4) – (−2)][a]	0.300
APACHE		22.5 [21–24][a]	24 [21–25][a]	0.347
SOFA		13 [11.75–14][a]	12.5 [11–14][a]	0.923
Candida		2.5 [2–3][a]	2 [2–2.25][a]	0.066
GCS		7 [6–8][a]	7 [5.75–8][a]	0.536
NIHSS		37 [35–39][a]	37 [34.75–39][a]	0.911

ALT Alanine aminotransferase, *APACHE* Acute Physiology and Chronic Health Evaluation, *AST* Aspartate aminotransferase, *BMI* Body mass index, *BUN* Blood urea nitrogen, *CRP* C-reactive protein, *EGF* Epidermal growth factor, *FBS* Fasting blood sugar, *GCS* Glasgow Coma Scale, *Hb* Hemoglobin, *IgA* Immunoglobulin A, *IgG* Immunoglobulin G, *IL-6* Interleukin 6, *IL-8* Interleukin 8, *K* Potassium, *kg* kilogram, *MgSO4* Magnesium sulfate, *ml* milliliter, *Na* Sodium, *NGAL* Neutrophil gelatinase-associated lipocalin, *NIHSS* National Institutes of Health Stroke Scale, *PAF* Platelet- activating factor, *PAI* Plasminogen activator inhibitor, *pg* Picogram, *PLT* Platelet, *RASS* Richmond Agitation-Sedation Scale, *S100B* S100 calcium binding protein B, *Scr* Serum creatinine, *SNSE* Serum neuron-specific enolase, *Sofa* Sequential Organ Failure Assessment, *T.Bill* Total bilirubin, *TGF* Transforming growth factor, *WBC* White blood cell, *Y* Years, Values are expressed as mean ± SD, * = statistically significant, a = Values which expressed as Median [IQR]

Table 28.2 Pre vs. Post comparison in each group

	MgSO4 (N = 18)			Placebo (N = 18)		
	Before	After	P value	Before	After	P value
IL-6 (pg/ml)	9.89 ± 2.79	6.94 ± 2.39	0.000*	8.33 ± 1.33	7.67 ± 1.411	0.131
IL-8 (pg/ml)	25.06 ± 4.39	16.89 ± 4.92	0.000*	13 ± 1.53	13.17 ± 2.92	0.810
FBS (mg/dl)	188.78 ± 70.06	180.17 ± 59.97	0.703	172.78 ± 93.95	174.89 ± 66.52	0.933
SNSE (µg/L)	12 ± 2.52	9.89 ± 2.93	0.011*	8.39 ± 1.2	8 ± 0.97	0.130
S100B (pg/ml)	11.83 ± 2.15	9 ± 2.87	0.007*	12.67 ± 1.37	12.56 ± 1.76	0.749
PAF (ng/ml)	95.11 ± 24.79	81.83 ± 25.05	0.005*	43.39 ± 14.79	38.22 ± 18.67	0.045*
PAI (ng/ml)	67.39 ± 26.79	64.78 ± 22.75	0.627	12.11 ± 5.50	13.67 ± 4	0.167
NGAL (ng/ml)	212.39 ± 53.49	193.11 ± 39.32	0.034*	207.22 ± 52.83	211.72 ± 55.13	0.627
EGF (pg/ml)	87.56 ± 36.41	67.28 ± 31.76	0.002*	88.56 ± 36.77	88.61 ± 39.7	0.994
TGF(pg/ml)	10.72 ± 5.68	10.56 ± 5.97	0.929	18.67 ± 8.98	19.56 ± 6.45	0.537
IgA (mg/dl)	7.56 ± 1.65	7.56 ± 1.2	1.000	7 ± 1.46	6.89 ± 1.41	0.726
IgG (mg/dl)	58.06 ± 15.74	52.67 ± 13.89	0.022*	28.33 ± 6	27.06 ± 5.33	0.221
WBC (cells//µl)	7.78 ± 2.29	7.06 ± 1.59	0.283	7.78 ± 1.44	8.06 ± 2.34	0.598
PLT (Plt/µl)	158.11 ± 32.30	167.11 ± 48.75	0.263	237.72 ± 60.39	185.83 ± 54.65	0.000 *
Hb (g/L)	10.28 ± 1.49	9.44 ± 1.5	0.031*	10.89 ± 1.41	10.83 ± 2.01	0.917
CRP (mg/L)	10.5 ± 2.07	8.83 ± 1.76	0.001*	11.67 ± 2.25	11.22 ± 3.06	0.631
ALT (mg/dl)	28.78 ± 4.7	27.94 ± 3.52	0.570	26.94 ± 11.02	26.61 ± 10.43	0.402
AST (mg/dl)	23.61 ± 4.23	24.61 ± 3.68	0.502	19.06 ± 5.33	18.83 ± 4.13	0.756
BUN (mg/dl)	23.22 ± 3.39	22.94 ± 3.08	0.749	18 ± 1.46	18.17 ± 1.25	0.660
Scr (mg/dl)	1.56 ± 0.57	1.4 ± 0.52	0.204	1.44 ± 0.35	1.28 ± 0.33	0.143
T.Bill (mg/dl)	1.20 [1–1.7] [a]	1 [0.9–1.28] [a]	0.021*	1 [1–2] [a]	1 [1–2][a]	0.848
Na (mEq/L)	141.94 ± 4.67	142.44 ± 5.09	0.760	143.11 ± 12.1	141.11 ± 6.2	0.522
K (mEq/L)	4.72 ± 0.81	4.58 ± 1.08	0.639	4.37 ± 0.73	4 ± 0.47	0.038
Lactate (mg/dl)	1.59 ± 0.61	1.61 ± 0.61	0.890	2 [1–3][a]	2 [1–2][a]	0.166
RASS	(−3) [(−4) – (−2)][a]	(−2) [(−3) – (−1.75)][a]	0.021*	(−3) [(−4) – (−2)] [a]	(−3) [(−3) – (−2)][a]	0.765
APACHE	22.5 [21–24][a]	19.5 [16.75–20][a]	0.000*	24 [21–25][a]	23 [21.75–25][a]	0.982
SOFA	13 [11.75–14][a]	11 [10.75–12][a]	0.005*	12.5 [11–14][a]	12 [11–13][a]	0.025*
Candida	2.5 [2–3][a]	2 [2–2][a]	0.013*	2 [2–2.25][a]	2 [1–2.25][a]	0.132
GCS	7 [6–8][a]	6 [5–7][a]	0.024*	7 [5.75–8][a]	6.5 [5–7.25] [a]	0.258
NIHSS	37 [35–39][a]	30.5 [29.75–37][a]	0.001*	37 [34.75–39][a]	37 [35–38.25]	0.877

ALT Alanine aminotransferase, *APACHE* Acute Physiology and Chronic Health Evaluation, *AST* Aspartate aminotransferase, *BUN* Blood urea nitrogen, *CRP* C-reactive protein, *EGF* Epidermal growth factor, *FBS* Fasting blood sugar, *GCS* Glasgow Coma Scale, *Hb* Hemoglobin, *IgA* Immunoglobulin A, *IgG* Immunoglobulin G, *IL-6* Interleukin 6, *IL-8* Interleukin 8, *K* Potassium, *kg* kilogram, *MgSO4* Magnesium sulfate, *ml* milliliter, *Na* Sodium, *NGAL* Neutrophil gelatinase-associated lipocalin, *NIHSS* National Institutes of Health Stroke Scale, *PAF* Platelet- activating factor, *PAI* Plasminogen activator inhibitor, *pg* Picogram, *PLT* Platelet, *RASS* Richmond Agitation-Sedation Scale, *S100B* S100 calcium binding protein B, *Scr* Serum creatinine, *SNSE* Serum neuron-specific enolase, *Sofa* Sequential Organ Failure Assessment, *T.Bill* Total bilirubin, *TGF* Transforming growth factor, *WBC* White blood cell, *Y* Years, Values are expressed as mean ± SD, * = statistically significant, a = Values which expressed as Median [IQR]

Table 28.3 Mean changes between MgSO4 group and placebo group

	Mean change		
	MgSO4	Placebo	P value
IL-6 (pg/ml)	−2.94 ± 2.04	−0.67 ± 1.78	0.001*
IL-8 (pg/ml)	−8.17 ± 6.83	0.17 ± 2.9	0.000*
FBS (mg/dl)	−8.61 ± 94.12	2.11 ± 105.09	0.749
SNSE (μg/L)	(−3) [(−4) – (1.25)][a]	(−1) [(−1) – (1)][a]	0.016*
S100B (pg/ml)	(−4) [(−6.5) – (−1)][a]	(−1) [(−1) – (1)][a]	0.003*
PAF (ng/ml)	−13.28 ± 17.62	−5.17 ± 10.11	0.099
PAI (ng/ml)	−2.61 ± 22.37	1.56 ± 4.57	0.449
NGAL (ng/ml)	−19.28 ± 35.54	4.5 ± 38.56	0.063
EGF (pg/ml)	−20.28 ± 23.17	0.06 ± 32.4	0.037*
TGF(pg/ml)	−0.17 ± 7.79	0.89 ± 5.99	0.651
IgA (mg/dl)	0 [0–0.25][a]	0 [(−1) – (1)][a]	0.857
IgG (mg/dl)	−5.39 ± 9.06	−1.28 ± 4.27	0.094
WBC (cells//μl)	−0.72 ± 2.76	0.28 ± 2.19	0.237
PLT (PLT/μl)	9 ± 32.95	−51.89 ± 45	0.000*
Hb (g/L)	(−1) [(−2) – (−0.5)][a]	0.5 [(−1.25) – (1)][a]	0.213
CRP (mg/L)	−1.67 ± 1.71	−0.44 ± 3.85	0.231
ALT (mg/dl)	−0.83 ± 6.1	−0.33 ± 1.64	0.741
AST (mg/dl)	1 ± 6.18	−0.22 ± 2.98	0.457
BUN (mg/dl)	−0.28 ± 3.63	0.17 ± 1.58	0.638
Scr (mg/dl)	−0.16 ± 0.5	−0.16 ± 0.45	0.972
T.Bill (mg/dl)	(−0.2) [(−0.63) – (−0.03)][a]	0 [(−1) – (1)][a]	0.252
Na (mEq/L)	0.5 ± 6.84	−2 ± 12.98	0.474
K (mEq/L)	−0.14 ± 1.28	−0.37 ± 0.7	0.515
Lactate (mg/dl)	0.02 ± 0.67	−0.28 ± 0.83	0.240
RASS	1 [0–2] [a]	0 [(−1) – (1)][a]	0.038*
APACHE	(−3.5) [(−6) – (−2)][a]	0 [(−2) – (2)][a]	0.000*
SOFA	(−2) [(−3) – (−1)][a]	(−1) [(−1.25) – (−0.5)][a]	0.054
Candida	(−1) [(−1) – (0)][a]	0 [(−1) – (0)][a]	0.335
GCS	(−1) [(−1.25) – (−0.5)][a]	(−1) [(−1) – (1)][a]	0.348
NIHSS	(−4.5) [(−8.25) – (−1.75)][a]	(−1) [(−2) – (2)][a]	0.002*

ALT Alanine aminotransferase, *APACHE* Acute Physiology and Chronic Health Evaluation, *AST* Aspartate aminotransferase, *BUN* Blood urea nitrogen, *CRP* C-reactive protein, *EGF* Epidermal growth factor, *FBS* Fasting blood sugar, *GCS* Glasgow Coma Scale, *Hb* Hemoglobin, *IgA* Immunoglobulin A, *IgG* Immunoglobulin G, *IL-6* Interleukin 6, *IL-8* Interleukin 8, *K* Potassium, *kg* kilogram, *MgSO4* Magnesium sulfate, *ml* milliliter, *Na* Sodium, *NGAL* Neutrophil gelatinase-associated lipocalin, *NIHSS* National Institutes of Health Stroke Scale, *PAF* Platelet- activating factor, *PAI* Plasminogen activator inhibitor, *pg* Picogram, *PLT* Platelet, *RASS* Richmond Agitation-Sedation Scale, *S100B* S100 calcium binding protein B, *Scr* Serum creatinine, *SNSE* Serum neuron-specific enolase, *Sofa* Sequential Organ Failure Assessment, *T.Bill* Total bilirubin, *TGF* Transforming growth factor, *WBC* White blood cell, *Y* Years, Values are expressed as mean ± SD, * = statistically significant, a = Values which expressed as Median [IQR]

28.3.5 Effect of MgSO4 on Prevention of Organ Failure

Using of MgSO4 can significantly improve the RASS (P = 0.021), Candida (P = 0.013) and Sofa (P = 0.005) scores of patients, though Sofa score (P = 0.025) was significantly improved in placebo group as well (Table 28.2). MgSO4-mediated elevation of RASS was just significantly higher when compared with placebo (P = 0.038) (Table 28.3).

28.3.6 Effect of MgSO4 on Neurological Improvement

Using of MgSO4 could significantly improve the NIHSS (P = 0.001), while significantly reduced the GCS (P = 0.024) (Table 28.2). MgSO4-mediated reduction of NIHSS was just significantly higher when compared with placebo (P = 0.002) (Table 28.3).

28.3.7 Effect of MgSO4 on Morbidity and Mortality in Stroke Patients

Using of MgSO4 may significantly improve the APACHE score (P < 0.001), which was not statistically changed in placebo group (P > 0.05) (Table 28.2), and MgSO4-mediated reduction of APACHE score was significantly higher when compared with placebo (P < 0.001) (Table 28.3). Although there was no death during the study, but 3 months after completion of the study, 2 (11.1%) patients of MgSO4 group and 3 (16.7%) patients of placebo group died, which was not statistically significant between groups (P > 0.05) (Table 28.1).

28.4 Discussion

Significant positive effect of intravenous (IV) administrated MgSO4 on the outcome in patients with acute stroke was shown [21], though supportive effect of it in amiodarone-induced complications in these patients was not determined. Our results demonstrated the beneficial effects of MgSO4 in patients with stroke who were administered with amiodarone when compared with placebo. The present trial illustrated significant reduction in NGAL, Hb and T.Bill levels in MgSO4 group that were not different from placebo group, but failed to show significance of the observed reduction in levels of FBS, WBC, ALT, BUN, Scr, and K and observed elevation in the levels of PLT, AST, NA and lactate in MgSO4 group. It was probably due to the different baseline levels of them in MgSO4 group compared with placebo, especially AST, BUN and PLT. Such that, in placebo group because of higher baseline level of PLT, higher reduction of its level was occurred compared with MgSO4 group.

Since immunological pulmonary complications and adverse neurological effects were reported in amiodarone-treated patients [12], we investigated the efficacy of MgSO4 on amiodarone-induced inflammatory and immunological indicators in stroke patients. Our results showed a significant reduction of IgG levels in MgSO4 group, which was initially higher compared with placebo group, while having no statistical impact on the concentration of IgA. In addition, we demonstrated that treatment with MgSO4 results in a significant decline in serum levels inflammatory markers including IL-6, IL-8, SNSE, S100B**,** EGF, PAF and CRP while having no statistical impact on the concentrations of PAI as the main inhibitor of tPA and anti-inflammatory marker like TGF, which was initially higher in placebo group than MgSO4 group. It was shown that SNSE level, a marker for neuronal damage whose reduction was significantly higher in MgSO4 group compared with placebo in our study, was associated with obesity and BMI > 25 [22], as our results showed that weight and BMI (>25) were significantly higher in MgSO4 group than placebo. The reduction in SNSE suggested to be due to impaired glucose metabolism and neuronal differentiation [22], though our results failed to show significance of the observed reduction in levels of FBS.

Since the expected outcome in human clinical stroke trials is neurological and functional improvements [23], we also investigated the efficacy of MgSO4 on prevention of organ failure and neurological improvement. Our results revealed that using of MgSO4 may improve the RASS, Candida and Sofa scores of patients, though just RASS score was shown better recovery in MgSO4 group when compared with placebo. In this regard, one previous study showed that IV MgSO4 did not reduce disablement of patients at 3 months when given within 12 h of clinically diagnosed stroke [24]. In addition, Sofa score was significantly improved in placebo

group as well. Furthermore, treatment with MgSO4 resulted in an improvement of NIHSS and subsequently neurologic deficit improvement after 5 days compared with placebo. In this sense, Lampl et al. also illustrated the neurological improvement of AIS patients in MgSO4 group compared with placebo [21]. However, our results failed to show improvement in GCS, which was significantly reduced in MgSO4 group, but this reduction was not statistically different between groups.

The results of our trial illustrated that IV administration of MgSO4 improved APACHE score in stroke patients who were administered with amiodarone when compared with placebo. Although the effects of the MgSO4 on reduction in the early death number of patients compared with placebo was shown [25], we demonstrated that the number of patients who died 3 months after completion of study was not statistically different between groups and that might be due to the amiodarone administration of both groups in our study. Indeed, it was shown that IV MgSO4 did not reduce death at 3 months when given within 12 h of clinically diagnosed stroke [24]. Furthermore, Sleeswijk et al. reported that in critically ill patients with new-onset AF who were administered with MgSO4 and then with amiodarone, APACHE score and hospital mortality were both higher in Mg non-responders group than responders group, though this was not significant. The authors proposed that pretreatment with MgSO4 had beneficial effects to reduce APACHE score and restore sinus rhythm in these patients [18].

In conclusion, MgSO4 treatment in AIS patients, who were treated with amiodarone, showed improvement of inflammatory, immunological and neurological indicators and reduction of disability in AIS patients, and this therapeutic strategy may be considered as a promising therapy for these patients in order to reduce amiodarone-induced complications.

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