

ORIGINAL ARTICLE

Effect of intravenous magnesium sulfate on mortality in patients with severe acute asthma

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ABSTRACT

Background and objective: Intravenous magnesium sulfate is used as adjunctive therapy for severe asthma exacerbations. However, previous randomized controlled trials of the administration of intravenous magnesium sulfate for asthma exacerbations have shown mixed results, and no study has evaluated its effect on mortality in patients with life-threatening asthma. The objective of this study was to investigate the association between intravenous magnesium sulfate administration and mortality in patients with severe asthma.

Methods: Patients with severe asthma requiring intravenous corticosteroids and oxygenation were selected using the Japanese Diagnosis Procedure Combination inpatient database. One-to-one propensity score matching was performed between patients having received or not intravenous magnesium sulfate. Primary outcomes were 7-, 14- and 28-day mortalities. Secondary outcomes were total dose of intravenous corticosteroids during hospitalization, duration of mechanical ventilation and length of stay.

Results: Among 14 122 eligible patients, 619 received intravenous magnesium sulfate. Propensity score matching created a matched cohort of 599 pairs with and without intravenous magnesium sulfate. There were no significant differences between patients with and without intravenous magnesium sulfate in terms of 28-day mortality (1.3% vs 1.8%, $P = 0.488$), median total dose of intravenous corticosteroids (2400 mg vs 2400 mg, $P = 0.580$), median duration of mechanical ventilation (1 day vs 1 day, $P = 0.118$) and median length of stay (16 days vs 13 days, $P = 0.640$).

Conclusion: This study found no significant benefit of intravenous magnesium sulfate use in terms of mortality in patients with severe acute asthma.

Key words: asthma exacerbation, intravenous magnesium sulfate, mortality, propensity score matching.

SUMMARY AT A GLANCE

IV MgSO₄ is used as adjunctive therapy for severe asthma exacerbations despite a lack of strict evidence on effect. This large, nationwide, retrospective study found no significant association between the use of IV MgSO₄ and mortality in patients with severe acute asthma.

Abbreviations: ICD-10, International Classification of Diseases 10th Revision; IV MgSO₄, intravenous magnesium sulfate.

INTRODUCTION

Asthma exacerbations are treated primarily with oxygen administration, inhaled short-acting β_2 -agonists and systemic corticosteroids,¹ with the addition of epinephrine according to asthma severity.² Intravenous magnesium sulfate (IV MgSO₄) has been regarded as an adjunctive therapy for severe and life-threatening asthma exacerbations.¹ However, the Global Strategy for Asthma and Management and Prevention 2014, which represents the global standard guidelines for asthma, did not recommend IV MgSO₄ for routine use in asthma exacerbations, but acknowledged that its use reduced hospital admissions in some patients.³

Previous randomized controlled trials have shown mixed results regarding the efficacy of IV MgSO₄ for asthma exacerbations. Some studies indicated that IV MgSO₄ had no significant effect on the proportion of patients requiring hospital admission,^{4–9} breathlessness^{5,10} or respiratory function,^{4–8,10,11} while others suggested that it improved respiratory function^{9,12,13} and hospital admission rates.^{12,13} One randomized controlled study concluded that IV MgSO₄ only reduced hospital admissions in patients with severe asthma.⁴ However, these studies only included patients with relatively less severe asthma who were able to undergo pulmonary function tests or report subjective symptoms. To the best of our knowledge, no study

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has yet assessed the mortality-reducing effects of IV MgSO₄ in patients with severe asthma exacerbations.

In the present study, we retrospectively collected data on patients with severe asthma exacerbations from a national inpatient database and performed a propensity score analysis to examine the association between IV MgSO₄ administration and reduction in mortality from severe asthma.

METHODS

Data source

The Diagnosis Procedure Combination database is a Japanese national database containing administrative claims data and discharge records. In 2012, the database had approximately 1000 participating hospitals, including all 82 academic hospitals, accounting for seven million inpatient records annually and representing 50% of all acute hospitalizations in Japan. The available data include unique hospital identifiers; patient age and sex; dates of admission and discharge; discharge status (dead or alive); diagnoses and comorbidities on admission and complications after admission recorded with text data in Japanese and the International Classification of Diseases 10th Revision (ICD-10) codes; pregnancy status; body height and weight; smoking status (pack-years); consciousness level at admission measured by the Japan Coma Scale;¹⁴ Hugh-Jones classification of respiratory status;¹⁵ names of drugs and devices and dates of use; and procedures. The Japan Coma Scale is categorized into four groups: 0 (alert), 1–3 (delirium), 10–30 (somnolence) and 100–300 (coma).¹⁴ The Hugh-Jones classification includes five grades of dyspnoea, based on the following criteria:¹⁵ (i) the patient's breathing is as good as that of other individuals of the same age and build when working, walking, and climbing hills or stairs (Grade 1); (ii) the patient is able to keep pace with healthy individuals of the same age and build on level ground, but unable to keep pace on hills or stairs (Grade 2); (iii) the patient is unable to keep pace with healthy individuals of the same age and build on level ground, but is able to walk about a mile or more at their own pace (Grade 3); (iv) the patient is unable to walk more than about 50 yards on level ground without rest (Grade 4); and (v) the patient is breathless on talking or undressing, or unable to leave house because of breathlessness (Grade 5).

We also extracted data on the types and doses of corticosteroids used during hospitalization, including hydrocortisone, methylprednisolone, prednisolone, triamcinolone, dexamethasone and betamethasone. Doses of intravenous corticosteroids were converted to hydrocortisone-equivalent doses.¹⁶

The requirement for informed consent was waived because of the anonymous nature of the data. This study was approved by the Institutional Review Board of the University of Tokyo.

Patient selection

We identified patients aged ≥15 years who were admitted to hospitals with a primary diagnosis of

'status asthmaticus' (ICD-10 code, J46) between July 2010 and March 2013. We excluded patients who were pregnant, had cardioversion at admission, acute myocardial infarction (I21, I22), acute subarachnoid haemorrhage (I60), myasthenia gravis (G70), dehydration (E86) or chronic obstructive pulmonary disease (J41–44). We focused on patients with severe asthma who received intravenous corticosteroids and oxygenation (oxygen inhalation or mechanical ventilation) within 2 days of admission. We divided these into patients who received IV MgSO₄ within 2 days of admission (IV MgSO₄ group) and those who did not (control group).

Covariates

The following factors were examined as covariates: age, sex, body mass index, smoking status, Japan Coma Scale on admission, Hugh-Jones classification on admission and respiratory comorbidities (including acute sinusitis (J01), influenza (J10–11), pneumonia (J12–18), vasomotor and allergic rhinitis (J30), chronic sinusitis (J32), interstitial pneumonia (J70, J84) and pneumothorax (J93)), heart failure (I50), renal failure (N17–19), theophylline use, epinephrine use, and mechanical ventilation. We defined hospital volume as the number of asthma exacerbation patients treated during the study period at each hospital. Hospital volume was divided into tertiles.

Outcomes

The primary outcomes were 7-, 14- and 28-day all-cause mortalities. The secondary outcomes were the total dose of intravenous corticosteroids during hospitalization (mg), length of stay (days) and duration of mechanical ventilation (days).

Statistical analysis

Proportions of categorical variables were compared using χ^2 tests, and averages or medians of continuous variables were compared between the groups using *t*-tests or Mann-Whitney *U*-tests. Outcomes in the IV MgSO₄ and control groups were compared by one-to-one propensity score matching to balance the baseline characteristics. Propensity scores were estimated using a logistic regression model for the recipients of IV MgSO₄ with adjustment for possible confounding variables, including patient age, sex, body mass index, smoking status, Hugh-Jones classification on admission, Japan Coma Scale score on admission, pre-existing comorbidities on admission, theophylline use, adrenaline use, mechanical ventilation and hospital volume. We created a category for patients with missing data, and used the direct method to input variables with missing data into the logistic regression model to create propensity scores. The C-statistic was used to evaluate the goodness of fit for the model. The C-statistic was calculated as the area under the receiver operating curve for the estimated propensity score and the actual usage of IV MgSO₄. Each patient in the IV MgSO₄ group was matched with a patient in the control group by nearest neighbour matching within a caliper (<0.20 of the pooled standard

deviation).¹⁷ Standardized differences were calculated to compare baseline covariates between the groups. An absolute standardized difference <10% was regarded as a meaningful imbalance in the baseline covariate.^{18,19}

Primary outcomes were compared between the propensity-matched groups using χ^2 tests, and secondary outcomes using *t*-tests or Mann–Whitney *U*-tests. The relative risks and the risk differences were calculated. We also performed subgroup analyses among the propensity score-matched patients to compare mortalities between patients with and without mechanical ventilation and with and without the use of epinephrine.

The threshold for significance was $P < 0.05$. All statistical analyses were performed using IBM SPSS version 22 (IBM, Armonk, NY, USA).

RESULTS

A total of 139 418 patients from 1168 hospitals were diagnosed as status asthmaticus (coded with ICD-10 code J46) during the 33-month study duration. Among them, 14 741 eligible patients from 1089 hospitals were categorized into the IV MgSO₄ group ($n = 619$) or control group ($n = 14 122$). Propensity score matching created 599 pairs. The C-statistic was 0.798 and the median length of stay was 15 days.

The baseline characteristics of the unmatched and propensity score-matched groups are shown in Table 1. Patients in the unmatched groups were more likely to receive IV MgSO₄ if they were younger, had coma, were admitted to a high-volume hospital, and required epinephrine or mechanical ventilation. The baseline characteristics were well balanced between the two groups after propensity score matching.

The overall 7-, 14- and 28-day mortalities were 0.46% (84 mortalities out of 18 101 patients), 0.86% (155 out of 18 101) and 1.3% (241 out of 18 101), respectively. There were significant differences in 7-, 14- and 28-day mortalities between the two groups in the unmatched analyses, but no significant differences in the propensity score-matched analyses (Table 2).

Relative risks and risk differences in 7-, 14- and 28-day mortalities in the propensity-matched groups are shown in Table 3. There were no significant differences in mortalities between the IV MgSO₄ and control groups.

The results of the subgroup analyses are shown in Table 4. There was no significant difference in 28-day mortality between the IV MgSO₄ and control groups in patients with and without mechanical ventilation or use of epinephrine.

In the propensity score-matched groups, there was no significant difference between the IV MgSO₄ and control groups in terms of median total dose of intravenous corticosteroids during hospitalization (2400 mg vs 2400 mg; $P = 0.580$), median duration of mechanical ventilation (1 day vs 1 day; $P = 0.118$) or median length of stay (16 days vs 13 days; $P = 0.640$).

DISCUSSION

This retrospective, large-scale study of 599 propensity score-matched pairs of patients with severe acute asthma found no significant association between IV MgSO₄ use and short-term mortality, in-hospital dose of intravenous steroids, length of stay, or duration of mechanical ventilation.

Most previous randomized controlled trials of IV MgSO₄ assessed its effects on the results of pulmonary function tests or preventing hospital admissions.^{4–13} The largest of these ($n = 1084$) was a three-armed trial comparing IV MgSO₄ with nebulized MgSO₄ and placebo. A lower proportion of patients in the IV MgSO₄ group required hospital admission compared with the placebo group, although the difference was not significant.⁵ Other small-sized studies ($n = 33–254$) showed mixed results.^{4,6–13} A meta-analysis reported that the frequency of admissions was reduced in patients with severe asthma receiving IV MgSO₄, but not in those with moderate asthma.²⁰ The Global Initiative for Asthma 2014 did not recommend routine use of IV MgSO₄, but suggested its limited use in patients who failed to respond to initial treatment and had persistent hypoxaemia.³ The Cochrane Review in 2014 showed that IV MgSO₄ significantly reduced hospital admissions and improved pulmonary function in adults with acute asthma who did not respond to initial treatment.²¹

However, all these studies excluded patients with severe asthma who were mechanically ventilated or who were unable to perform pulmonary function tests. To the best of our knowledge, the present study is the first to investigate the effects of IV MgSO₄ in such patients. Furthermore, no previous study has assessed the association between IV MgSO₄ and asthma death. The strength of this study was therefore its assessment of the mortality-reducing effect of IV MgSO₄ in patients with very severe asthma. Although the rarity of mortality due to asthma exacerbation makes it difficult to analyse, the use of a large, nationwide database enabled us to conduct this first investigation into the association between IV MgSO₄ and asthma death.

The propensity score-matched approach provides a powerful tool for creating a randomized trial-like situation, by comparing groups with similar observed characteristics without specifying the relationships between confounders and outcomes. In the unmatched groups, smokers were more likely to receive IV MgSO₄, suggesting that smokers were more likely to have severe asthma exacerbations. Before propensity score matching, patients in the IV MgSO₄ group were more likely to have coma and require epinephrine or mechanical ventilation, presumably reflecting the fact that physicians were more likely to prescribe IV MgSO₄ in these patients with more severe disease. Such confounding could affect the significance of differences in unadjusted mortalities between the unmatched groups, while one-to-one propensity score matching successfully balanced the baseline characteristics between the groups with and without IV MgSO₄, thereby reducing the confounding bias.

Table 1 Backgrounds of patients with and without magnesium infusion in unmatched and propensity-matched groups

	Unmatched groups			Propensity-matched groups		
	Without IV MgSO ₄	With IV MgSO ₄	Standardized difference	Without IV MgSO ₄	With IV MgSO ₄	Standardized difference
Total (n)	14 122	619	—	599	599	—
Age (years), average	57.54	52.88	-0.2	53.21	52.97	0.0
Sex (male), n (%)	5326 (37.7)	273 (44.1)	13.0	259 (43.2)	264 (44.1)	1.7
Body mass index (kg/m ²), n (%)						
18.5–24.9	6639 (47.0)	273 (44.1)	-5.8	276 (46.1)	266 (44.4)	-3.4
<18.5	1522 (10.8)	71 (11.5)	2.2	67 (11.2)	69 (11.5)	1.1
25.0–29.9	2569 (18.2)	109 (17.6)	-1.5	107 (17.9)	105 (17.5)	-0.9
≥30.0	1303 (9.2)	61 (9.9)	2.1	58 (9.7)	59 (9.8)	0.6
Missing	2089 (14.8)	105 (17.0)	5.9	91 (15.2)	100 (16.7)	4.1
Smoking status, n (%)						
Non-smoker	7338 (52.0)	265 (42.85)	-18.2	275 (45.9)	259 (43.2)	-5.4
Smoker	5217 (36.9)	259 (41.8)	10.0	233 (38.9)	250 (41.47)	5.8
Missing	1567 (11.1)	95 (15.3)	12.5	91 (15.2)	90 (15.0)	-0.5
Theophylline, n (%)	7612 (53.9)	246 (39.7)	-28.1	235 (39.2)	243 (40.6)	2.7
Epinephrine, n (%)	1568 (11.1)	250 (40.4)	63.5	227 (37.9)	231 (38.6)	1.4
Respiratory comorbidities, n (%)	3201 (22.7)	153 (24.7)	4.8	136 (22.7)	146 (24.4)	3.9
Chronic heart failure, n (%)	1536 (10.9)	52 (8.4)	-8.4	61 (10.2)	49 (8.2)	-6.9
Chronic renal failure, n (%)	208 (1.5)	4 (0.6)	-8.1	5 (0.8)	4 (0.7)	-1.9
Japan Coma Scale at admission, n (%)						
Alert	12 870 (91.1)	472 (76.3)	-39.5	467 (78.0)	470 (78.5)	1.2
Dizziness	865 (6.1)	71 (11.5)	18.8	69 (11.5)	65 (10.9)	-2.1
Somnolence	204 (1.4)	24 (3.9)	15.1	25 (4.2)	22 (3.7)	-2.6
Coma	183 (1.3)	52 (8.4)	32.6	38 (6.3)	42 (7.0)	2.7
Hugh-Jones classification, n (%)						
1	1896 (13.4)	105 (17.0)	9.8	85 (14.2)	103 (17.2)	8.3
2	1812 (12.8)	73 (11.8)	-3.2	80 (13.4)	70 (11.7)	-5.0
3	1646 (11.7)	55 (8.9)	-9.1	56 (9.3)	55 (9.2)	-0.6
4	3196 (22.6)	92 (14.9)	-19.8	105 (17.5)	88 (14.7)	-7.7
5	4083 (28.9)	224 (36.2)	15.5	209 (34.9)	217 (36.2)	2.8
Missing	1489 (10.5)	70 (11.3)	2.5	64 (10.7)	66 (11.0)	1.1
Mechanical ventilation, n (%)	714 (5.1)	206 (33.3)	67.5	191 (31.9)	186 (31.1)	-1.8
Hospital volume (year), n (%)						
≤89	4436 (31.4)	75 (12.1)	-45.5	64 (10.7)	74 (12.4)	5.2
90–237	4541 (32.2)	225 (36.3)	8.8	221 (36.9)	220 (36.7)	-0.3
≥238	5145 (36.4)	319 (51.5)	30.1	314 (52.4)	305 (50.9)	-3.0
IV, intravenous.						

Table 2 Seven-, 14- and 28-day mortalities with and without magnesium infusion in unmatched and propensity-matched groups

	Unmatched groups			Propensity-matched groups		
	Without IV MgSO ₄ (n = 14 122)	With IV MgSO ₄ (n = 619)	P	Without IV MgSO ₄ (n = 599)	With IV MgSO ₄ (n = 599)	P
28-day mortality	162 (1.1)	13 (2.1)	0.032	8 (1.3)	11 (1.8)	0.488
14-day mortality	101 (0.7)	11 (1.8)	0.003	6 (1.0)	9 (1.5)	0.436
7-day mortality	55 (0.4)	8 (1.3)	0.001	3 (0.5)	6 (1.0)	0.315

Data are presented as n (%).

IV, intravenous.

Table 3 Relative risk and risk difference of 7-, 14- and 28-day mortalities in propensity-matched group

	Relative risk	95% confidence interval	Risk difference	95% Confidence interval
28-day mortality	1.38	0.06–3.39	0.005	–0.009 to 0.019
14-day mortality	1.50	0.54–4.19	0.005	–0.008 to 0.018
7-day mortality	2.00	0.50–7.96	0.005	–0.005 to 0.015

Table 4 Subgroup analyses of 28-day mortality rates in propensity-matched groups

	Without IV MgSO ₄	With IV MgSO ₄	Odds ratio (95% confidence interval)
With mechanical ventilation	3.1% (6/191)	4.3% (8/186)	1.4 (0.5–4.0)
Without mechanical ventilation	0.5% (2/408)	0.7% (3/413)	1.5 (0.2–8.9)
With epinephrine	2.2% (5/227)	4.3% (10/231)	2.0 (0.7–5.8)
Without epinephrine	0.8% (3/372)	0.3% (1/368)	0.3 (0.03–3.3)

IV, intravenous.

There were several limitations to this study. First, although we used a nationwide database, this was a retrospective, observational study, without randomization. Despite the use of the propensity score method to adjust the baseline characteristics, bias could still occur as unmeasured confounders that increase the risk of asthma-related death, such as past history of intubation, history of hospitalization, history of oral and inhaled corticosteroid use, history of overuse of short-acting β_2 -agonists, history of psychiatric disease or psychosocial problems, poor adherence to asthma medications, and the presence of food allergies.³ Second, patients who died in the emergency outpatient unit were not included, even if they received IV MgSO₄, because the Diagnosis Procedure Combination database only contains inpatient information. However, this lack of information may not necessarily affect the results because most asthma patients who die in the emergency outpatient unit are dead on arrival,²² and most asthma patients who leave the emergency outpatient unit have mild asthma, and such patients would thus be unlikely to be considered as candidates for IV MgSO₄ administration. Third, we defined severe asthma patients as

having a diagnosis of ‘status asthmaticus’ (ICD-10 code, J46) on admission, and received IV corticosteroids and oxygenation within 2 days of admission. Although the Global Strategy for Asthma and Management and Prevention 2014 recommends MgSO₄ in adults with forced expiratory volume in 1 s <25–30% or who have persistent hypoxaemia, the database did not contain information on these clinical parameters. Furthermore, the recorded diagnoses in the present retrospective study may have been less accurate than those in planned prospective studies. Finally, because this study was conducted using an inpatient database, we had no information on the use of drugs that were prescribed before admission and then used during hospitalization (such as inhalers).

In conclusion, the present propensity-matched analysis using a large, nationwide database found no significant benefit of IV MgSO₄ on 7-, 14- and 28-day mortalities in patients hospitalized with severe asthma. This suggests that IV MgSO₄ use should not be recommended in these patients. However, further prospective, randomized trials are required to clarify the effects of IV MgSO₄ on severe asthma-related mortality.

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