

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of Intravenous Magnesium Sulfate among Patients with Acute Myocardial Infarction in China from 2001 to 2015: China PEACE-Retrospective AMI Study
AUTHORS	Wang, Xianqiang; Du, Xue; Yang, Hao; Bucholz, Emily; Downing, Nicholas; Spertus, John; Masoudi, Fredrick; Li, Jing; Guan, Wenchi; Gao, Yan; Hu, Shuang; Bai, Xueke; Krumholz, Harlan; Li, Xi

VERSION 1 – REVIEW

REVIEWER	Vincenzo Lionetti Scuola Superiore Sant'Anna, Italy
REVIEW RETURNED	25-Sep-2019

GENERAL COMMENTS	<p>Wang et al have performed an interesting study to investigate the scenario supporting the partial de-adoption of an established medical treatment, such as IV magnesium sulphate, even if evidence of related lethal effects are clear and evidence-based. Some issues should be clarified.</p> <p>Major issues</p> <ol style="list-style-type: none">1) It is clinically relevant to evaluate the relationship between the dose of IV magnesium sulphate and its current use in hospital setting.2) Another relationship that should be investigated is whether patients still treated with IV magnesium sulphate received or not thrombolytic therapy.3) The authors should better characterize the use of IV magnesium sulphate despite the magnitude of left ventricular ejection fraction and onset of acute heart failure.4) Interesting are the co-medications. In order to better understand the use of intravenous magnesium sulphate, the authors should better describe the relationship between magnesium sulphate de-adoption and particular association with drugs (i.e.: aminophylline)
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REVIEWER	Ovidiu Chioncel UMF Carol Davila, Bucharest Romania
REVIEW RETURNED	07-Dec-2019

GENERAL COMMENTS	<p>One of the most curious issue is the high rate of use of Magnesium in patients from teaching hospitals and tertiary hospitals.</p> <p>I would add some sentences at Discussion section about the imperious need for education measures.</p>
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REVIEWER	Min Zhao University Medical Centre, Utrecht, Netherlands
REVIEW RETURNED	17-Dec-2019

GENERAL COMMENTS	<p>That is a very interesting topic discussing the use of intravenous magnesium sulfate among patients with acute myocardial infarction in China.</p> <p>Abstract: This study aims to evaluate the variation of the use of intravenous magnesium sulfate in different regions. I would expect more information on patient characteristics in abstract (i.e. mean age, % of women, and number of patients in each study year/region etc).</p> <p>Introduction: Author stated that Chinese guideline was published in 2001 to against the use of IV magnesium and one of their aims is to investigate trend of intravenous magnesium sulfate use after Chinese guideline amended. It may be worth to include previous situation before 2001 and show differentiation and how guideline has be implemented.</p> <p>Method: in study sample, it stated that 'we were unable to exclude patients with hypomagnesemia because magnesium levels were not collected'. Have this been properly discussed in limitation? Have this been adjusted from analysis? How many/% of confirmed hypokalemia have been excluded? Any different between patient characteristics?</p> <p>Statistical analysis: Please indicate in manuscript what have been adjusted. In figure 1, there is dose difference. Has this also been adjusted?</p> <p>Results:</p> <p>More information from table 1 is needed for baseline data, like number of patients divided by different geographical area, % of smoker or diabetes, etc. Any information on rural and urban area?</p>
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	<p>In the second paragraph of result, it focuses on patient and hospital characteristics associated with IV magnesium sulfate use. Some basic patient characteristics have not been reported. Like: age, gender, and hospital type. Also, have cardiovascular medication been reported, especially insufficient use of cardiovascular medication may lead recurrent of cardiac event and complications?</p> <p>In terms of outcome, has dose effect been considered? What is the impact?</p> <p>Discussion:</p> <p>As it discussed, the changes of Chinese guideline may lead to different clinical performance. Is there any supportive evidence? Could you compare the changes/trends before and after 2001?</p> <p>More deep limitations should be addressed. For example lack of full patient characteristics information and adjustment. And, as it aims to assess trends of IV magnesium use, why there is no consistent information for years between 2001 and 2015? Could you explain why you would only focus on these four years?</p> <p>Reference: please update some references with most recent research.</p>
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VERSION 1 – AUTHOR RESPONSE

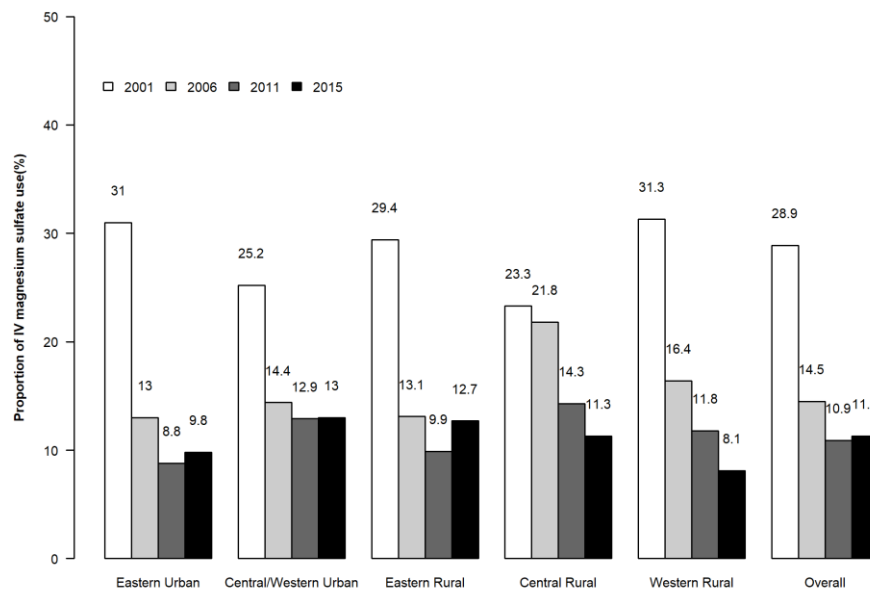
Reviewer #1: Wang et al have performed an interesting study to investigate the scenario supporting the partial de-adoption of an established medical treatment, such as IV magnesium sulphate, even if evidence of related lethal effects are clear and evidence-based. Some issues should be clarified.

Response: We appreciate this comment.

Comment 1: It is clinically relevant to evaluate the relationship between the dose of IV magnesium sulphate and its current use in hospital setting.

Response: We appreciate the comment and agree that an analysis incorporating dose could make the findings more robust. Although dosage data were not available, we hypothesized that multiple dose of magnesium sulfate was more likely to be a routine administration compared with the single dose that is commonly used for repletion or arrhythmias. Thus, we conducted a sensitivity analysis focusing on multiple dose. The results were added in the text on Page 12, Line 18-22 as below, as well as in the appendix.

There was a significant decrease in the multiple use of IV magnesium sulfate, from 28.9% in 2001 to 14.5% in 2006, 10.9% in 2011 and 11.31% in 2015 ($p < .001$ for trend). Nearly identical predictors of IV magnesium sulfate use were found when we compared patients receiving multiple doses to those without IV magnesium sulfate (appendix).



Comment 2: Another relationship that should be investigated is whether patients still treated with IV magnesium sulphate received or not thrombolytic therapy.

Response: We agree with this comment, and believe that information would be important to develop quality improvement strategy (e.g. targeted staff education) in the future. In table 1, we already presented the data regarding the relationship between the use of IV magnesium sulphate and the reperfusion therapy. Further association analysis in a multivariable model was also showed in the text on Page 11, Line 20-23 as below. We would defer to further interests of the reviewer.

In the multivariable model, we demonstrate that receipt of reperfusion therapy (1.64 (1.38-1.94) for fibrinolytic therapy, 1.68 (1.44-1.97) for primary PCI, both $P < .0001$) were positively associated with IV magnesium sulfate use.

Comment 3: The authors should better characterize the use of IV magnesium sulphate despite the magnitude of left ventricular ejection fraction and onset of acute heart failure.

Response: We appreciate the comment. In this revision, we performed the univariate analysis and multivariable model to study the relationship between the IV magnesium sulphate and the presence of heart failure during hospitalization. The results show that patients with onset of acute heart failure were more likely to receive IV magnesium sulfate. We present this result on Page 11, Line 23-24 as below:

In the multivariable model....., and onset of heart failure (OR 1.69, 95% CI 1.37-2.09, $P < .001$) were positively associated with use of IV magnesium sulfate use.

Our study collected information of prior hospitalizations based on the medical records. Thus, there were around 50% of medical records with no documented left ventricular ejection fraction, because the examination had not been conducted. Moreover, this proportion differed across hospitals and over time. We thus did not exam the relationship between use of IV magnesium sulphate and left ventricular ejection fraction.

Comment 4: Interesting are the co-medications. In order to better understand the use of intravenous magnesium sulphate, the authors should better describe the relationship between magnesium sulphate de-adoption and particular association with drugs (i.e.: aminophylline)

Response: We appreciate the comment. We had conducted analysis on relationship between use of IV magnesium sulphate and primary PCI or fibrinolytic therapy, and in this revision, we added relationships between use of IV magnesium sulphate and other routine co-medications for AMI, including aspirin, clopidogrel, beta-blockers, ACEI/ARB, and statins. The results were showed in the text on Page 11, Line 21-24 as below:

In the multivariable model, we demonstrate that receipt of aspirin within 24h (1.43(1.22-1.67), statin use (1.33(1.13-1.57), receipt of reperfusion therapy (1.64 (1.38-1.94) for fibrinolytic therapy, 1.68 (1.44-1.97) for primary PCI, both $P < .0001$) were positively associated with IV magnesium sulfate use.

However for aminophylline particularly, we had not extracted information on its use from the medical records, since this study was designed to assess treatment patterns for AMI, so potential co-medications for other conditions like aminophylline were not included. Thus, we

could not examine the relationship between magnesium sulphate de-adoption and use of aminophylline.

Reviewer #2

Comment 1: One of the most curious issues is the high rate of use of Magnesium in patients from teaching hospitals and tertiary hospitals. I would add some sentences at Discussion section about the imperious need for education measures.

Response: We agree with the comment. To be clear, the data showed in table 1 is the proportion of subgroups in all patients using or not using IV magnesium sulphate. The results showed that there was no significant difference in use based upon the teaching status, economic geographic region and rural/urban of hospitals (Page 11, line 25-26). However, the fact that teaching hospitals and tertiary hospitals were not performing better than non-teaching and secondary hospitals should also be alarming. We add sentences in discussion section to highlight this result on page 14 line 2-4 as below:

On the one hand, magnesium sulfate using in 2015 The teaching status or tertiary level did not translate into the better performance in this measure, which underscores the widespread need for continued education and evaluation of clinical practice.

Reviewer #3 That is a very interesting topic discussing the use of intravenous magnesium sulfate among patients with acute myocardial infarction in China.

Response: We appreciate this comment.

Comment 1: Abstract: This study aims to evaluate the variation of the use of intravenous magnesium sulfate in different regions. I would expect more information on patient characteristics in abstract (i.e. mean age, % of women, and number of patients in each study year/region etc.).

Response: We agree with the comment. Due to the space limits, we could not add all patient-level information in the abstract. Please see on Page 10, line 8-12 as below:

After excluding patients with hypokalemia (<3.5 mmol/L, n= 3,790), 24,418 patients remained, including, in the four study years, including 2,073 in 2001, 3,888 in 2006, 8,117 in 2011 and 10,340 in 2015. Almost half (41.2%) of the patients were hospitalized in rural areas. The average age was 65.1±12.7years, 29.7% were female.

Comment 2: Introduction: Author stated that Chinese guideline was published in 2001 to against the use of IV magnesium and one of their aims is to investigate trend of intravenous magnesium sulfate use after Chinese guideline amended. It may be worth to include previous situation before 2001 and show differentiation and how guideline has be implemented.

Response: Our study is the first nationally representative study, to our knowledge, to characterize the rate of IV magnesium sulfate in patients with AMI in China. Our first-year data that was collected in 2001 might be reasonable to seen as the “previous situation”, since it was the year of the Chinese guideline amendment. Additionally, in this revision, we cited a prior study conducted in 1998 on use of IV magnesium sulfate for AMI in China on Page 13, Line 11-13 to show previous situation, even it was a questionnaire study for physician regarding the management for AMI.

Questionnaire for chief cardiologist from 2500 hospital in China in 1998 revealed that 47% of physician would prescribe magnesium sulfate for patients with AMI.¹

Comment 3: Method: in study sample, it stated that ‘we were unable to exclude patients with hypomagnesaemia because magnesium levels were not collected’. Have this been properly discussed in limitation? Have this been adjusted from analysis? How many/% of confirmed hypokalemia have been excluded? Any different between patient characteristics?

Response: We appreciate this comment. We discussed this in the first point in the limitation section on page 15, line 11-14 as below:

First, we could not exclude patients with some indications, such as hypomagnesaemia and episodes of Torsade de pointes. However, we estimate that the influence is relatively small given low prevalence of these conditions previously reported.²

There are 3790 patients with hypokalemia (<3.5mmol/L) were excluded. The characteristics of these patients are showed in the table below. Baseline characteristics of patients with or without hypokalemia (study cohort) were comparable. Among the patients with hypokalemia, those receiving IV magnesium sulfate were more likely to have cardiac arrest at presentation, receive reperfusion therapy, be at urban hospital, or be in Central or Western regions, which is similar with the situation in patients without hypokalemia. We also present this table in the appendix.

Characteristics	Overall	Use N(%)	Non-Use(%)	P value
Patient characteristics				
Age				0.005
<55	753(19.9)	170(20)	583(19.8)	
55-64	873(23.0)	225(26.5)	648(22.0)	
65-74	1135(29.9)	260(30.6)	875(29.8)	
>=75	1029(27.2)	195(22.9)	834(28.4)	
Gender				0.621
Female	1508(39.8)	332(39.1)	1176(40.0)	
Male	2282(60.2)	518(60.9)	1764(60.0)	
Hypertension	2318(61.2)	547(64.4)	1771(60.2)	0.060
Diabetes	655(17.3)	131(15.4)	524(17.8)	0.101
Dyslipidemia	212(5.6)	38(4.5)	174(5.9)	0.106
Currently smoking	1170(30.9)	286(33.6)	884(30.1)	0.057
Prior ischemic stroke	452(11.9)	102(12.0)	350(11.9)	0.940
Prior myocardial infarction	325(8.6)	91(10.7)	234(8.0)	0.012
Prior CABG/PCI	97(2.6)	23(2.7)	74(2.5)	0.759
Chest discomfort	3380(89.2)	764(89.9)	2616(89)	0.455
Left branch block at presentation	59(1.6)	16(1.9)	43(1.5)	0.384
Cardiac arrest at presentation	80(2.1)	28(3.3)	52(1.8)	0.006
Cardiogenic shock at presentation	306(8.1)	83(9.8)	223(7.6)	0.040
Acute stroke at presentation	102(2.7)	16(1.9)	86(2.9)	0.098
Heart rate at presentation, bpm				0.457
<50	163(4.3)	36(4.2)	127(4.3)	
50-110	3331(87.9)	739(86.9)	2592(88.2)	
>110	296(7.8)	75(8.8)	221(7.5)	
SBP at presentation, mmHg				0.046

<120	1263(33.3)	314(36.9)	949(32.3)	
120-139	1096(28.9)	223(26.2)	873(29.7)	
140-159	771(20.3)	162(19.1)	609(20.7)	
>=160	660(17.4)	151(17.8)	509(17.3)	
Reperfusion therapies				<0.001
No reperfusion	557(14.7)	156(18.4)	401(13.6)	
Fibrinolytic therapy	2809(74.1)	585(68.8)	2224(75.6)	
Primary PCI	424(11.2)	109(12.8)	315(10.7)	
Hospital characteristics				
Teaching hospital	3042(80.3)	707(83.2)	2335(79.4)	0.015
PCI capable hospital	2455(64.8)	581(68.4)	1874(63.7)	0.013
Hospital level				0.047
Secondary or lower	1507(39.8)	313(36.8)	1194(40.6)	
Tertiary hospital	2283(60.2)	537(63.2)	1746(59.4)	
Economic geographic region				0.682
Eastern	798(21.1)	184(21.6)	614(20.9)	
Central	2163(57.1)	474(55.8)	1689(57.4)	
Western	829(21.9)	192(22.6)	637(21.7)	
Urban/Rural				0.023
Rural	1739(45.9)	361(42.5)	1378(46.9)	
Urban	2051(54.1)	489(57.5)	1562(53.1)	

Comment 4: Statistical analysis: Please indicate in manuscript what have been adjusted. In figure 1, there is dose difference. Has this also been adjusted?

Response: We have added relevant information in this revision, to clarify the variables adjusted in the multivariable model on Page 8, Line 22-23, as follows:

All covariates showed in Table 1, except those with frequencies below 1%, were included in the multivariable model.

Regarding to the dose of IV magnesium, we performed a sensitivity analysis focusing on multiple doses use. We add this information in the analysis plan on Page 12, Line 18-23, and also included the detailed results in Appendix.

The sensitivity analysis showed that there was also a significant decrease in the multiple doses of IV magnesium sulfate, from 28.9% in 2001 to 14.5% in 2006, 10.9% in 2011 and 11.31% in 2015 ($p < .001$ for trend). Nearly identical predictors of IV magnesium sulfate use were found when we compared patients receiving multiple doses to those without IV magnesium sulfate (appendix).

Comment 5: Results: More information from table 1 is needed for baseline data, like number of patients divided by different geographical area, % of smoker or diabetes, etc. Any information on rural and urban area?

Response: Due to the space limit, we did not re-state each detailed number for the baseline characteristics. However, we did show that in Table 1. The number of patients is 13614 (55.8%) in Eastern region, 5886(24.1%) in central region and 4918(20.1%) in western region. Also, 41.2% and 58.8% of patients in our study were from rural and urban hospitals separately.

We did not include the information about smoking and diabetes due to the space limit, but we did summarize that “almost three quarters had at least one cardiac risk factors (hypertension, diabetes, dyslipidemia or smoking)” on Page 10, line 12-14 in the version we submitted.

Comment 6: In the second paragraph of result, it focuses on patient and hospital characteristics associated with IV magnesium sulfate use. Some basic patient characteristics have not been reported. Like: age, gender, and hospital type. Also, have cardiovascular medication been reported, especially insufficient use of cardiovascular medication may lead recurrent of cardiac event and complications?

Response: As showed in Table 1, variables that were not significantly associated with IV magnesium sulfate included age, genders, hospital characteristics and economic geographic region. In terms of the cardiovascular medicine, we appreciate the comment and added the medication treatment in Table 1 (see below). Medication treatments are also included in the multivariable model. The results were showed in the text on Page 11, Line 21-23 as below:

In the multivariable model, we demonstrate that receipt of aspirin within 24h (1.43(1.22-1.67), statin use (1.33(1.13-1.57))... were positively associated with IV magnesium sulfate use.

Characteristics	Overall	Use N (%)	Non-Use (%)	P value
Medication				
Aspirin within 24-hour	13742(56.3)	2688(61.2)	11054(55.2)	<0.001
ACE inhibitors or angiotensin receptor blockers within 24-hour	13662(56)	2541(57.8)	11121(55.5)	0.006
β-blockers within 24-hour	10051(41.2)	1768(40.2)	8283(41.4)	0.169
Clopidogrel within 24-hour	10572(43.3)	1845(42)	8727(43.6)	0.054
Statins within 24-hour	13031(53.4)	2398(54.6)	10633(53.1)	0.076

Comment 7: In terms of outcome, has dose effect been considered? What is the impact?

Response: We appreciate this comment. As suggested by the reviewer, we have included an additional analysis that examines the relationship between different dose of IV magnesium sulfate (non-use, one dose, and multiple dose) and the in-hospital outcomes. After adjusted for hospital characteristics, patient risk profiles, medications and reperfusion therapies, using propensity score matching, all in-hospital outcomes were not significant different between multiple dose and non-use of IV magnesium sulfate. However, the patients treated with single dose of IV magnesium sulfate had still higher risk for in-hospital death (OR 1.56, 95% CI 1.25-1.94, P< .001), in-hospital death or treatment withdraw (OR 1.72, 95% CI 1.40-2.11, P< .001), and in-hospital composite of major complications (OR 1.73, 95% CI 1.46-2.06, P< .001) .We presented the above detailed results in the appendix.

Comment 8: Discussion: As it discussed, the changes of Chinese guideline may lead to different clinical performance. Is there any supportive evidence? Could you compare the changes/trends before and after 2001?

Response: Our study is the first nationally representative study, to our knowledge, to characterize the rate of IV magnesium sulfate in patients with AMI in China. Our first-year data that was collected in 2001 might be reasonable to seen as the “previous situation”, since it was the year of the Chinese

guideline amendment. Additionally, in this revision, we cited a prior study conducted in 1998 on use of IV magnesium sulfate for AMI in China on Page 13, Line 11-13, even it was a questionnaire study for physician regarding the management for AMI, to show previous situation.

Questionnaire for chief cardiologist from 2500 hospital in China in 1998 revealed that 47% of physician would prescribe magnesium sulfate for patients with AMI.¹

Comment 9: More deep limitations should be addressed. For example lack of full patient characteristics information and adjustment. And, as it aims to assess trends of IV magnesium use, why there is no consistent information for years between 2001 and 2015? Could you explain why you would only focus on these four years?

Response: We thank the reviewer for this comment. We agree that residual confounding of measured or unmeasured variables might affect the observed results, even we included all available patient characteristics based on clinical judgment and literature review. Thus, we revised the limitation section to better clarify this as below on Page 15, line 24-26

Finally, residual confounding of measured or unmeasured variables might affect the observed results about in-hospital outcomes of patients with and without IV magnesium sulfate use.

For the timeframe, as a retrospective study, the China PEACE study firstly selected 2001, 2006 and 2011 reflect the 10-year (from 2001 to 2011) trend, given the limited resources. After a survey on the organizational learning culture of these hospitals in 2013, we decided to continually elucidate the treatment patterns and patient outcomes based on this unique nationally representative network, in order to serve the nationwide quality improvement. Thus data in 2015 was additionally collected using the consistent methods.

Comment 10: Reference: please update some references with most recent research.

Response: We added references about recent research in the section as below:

(Page 5, line 13-14) few have examined de-adoption of ineffective therapy in clinical practice.³⁻⁵
(Page 15, line 4-7) how to establish a system to report feedback periodically on the appropriateness of treatment by practitioners and hospitals, how to design an accountability-oriented mechanism to prohibit ineffective regimen being prescribed, etc.⁶

Reference

1. LX. J, ZM. C, JX. X, Collin. R, Peto. R, LS L. [Suvery of hospital of myocardial infarction in China]. *Linchuang XIn Xue Guan Bing Za Zhi*, 2002; (9): 417-20.
2. Shafiq A, Goyal A, Jones PG, et al. Serum Magnesium Levels and In-Hospital Mortality in Acute Myocardial Infarction. *J Am Coll Cardiol* 2017; 69(22): 2771-2.
3. Hauptman PJ, Schnitzler MA, Swindle J, Burroughs TE. Use of nesiritide before and after publications suggesting drug-related risks in patients with acute decompensated heart failure. *Jama* 2006; 296(15): 1877-84.
4. Sauro K, Bagshaw SM, Niven D, et al. Barriers and facilitators to adopting high value practices and de-adopting low value practices in Canadian intensive care units: a multimethod study. *BMJ open* 2019; 9(3): e024159.
5. Niven DJ, McCormick TJ, Straus SE, Hemmelgarn BR, Jeffs LP, Stelfox HT. Identifying low-value clinical practices in critical care medicine: protocol for a scoping review. *BMJ open* 2015; 5(10): e008244.

6. Niven DJ, Mrklas KJ, Holodinsky JK, et al. Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC medicine 2015; 13: 255.

VERSION 2 – REVIEW

REVIEWER	Vincenzo Lionetti Scuola Superiore Sant'Anna, Italy
REVIEW RETURNED	26-Jan-2020
GENERAL COMMENTS	I have not further questions.