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Does magnesium sulfate increase the incidence of postpartum hemorrhage? A systematic review

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ABSTRACT

The incidence of Postpartum Hemorrhage (PPH) is increasing in the western world. We hypothesize that magnesium sulfate ($MgSO_4$) could be a contributing factor. $MgSO_4$ might increase the incidence of PPH by induction of vasodilation, tocolytic effects, and effects on the blood like red cell deformity, platelet activity inhibition and a prolonged bleeding time. Based on these effects of $MgSO_4$ a correlation with PPH is suspected. $MgSO_4$ is widely used in the prevention of eclampsia. However, the working mechanism of this effective drug is largely unknown. We performed a systematic search to find all Randomized Controlled trials (RCTs) containing $MgSO_4$ in preeclamsia as well as all $MgSO_4$ studies with information on PPH. Titles, abstracts and references of publications were evaluated for appropriateness and whether they met the inclusion criteria. RCTs about $MgSO_4$ with original data on PPH prevalence were included in our systematic review. We calculated the relative risk of PPH in every study as well as an overall relative risk. Four relevant and valid RCTs were found, totalling 11,621 relevant patients. The relative risk of PPH in women treated with $MgSO_4$ is 0.964 (95% CI 0.886 - 1.050). In this systematic review we found no significant increase in PPH in women treated with $MgSO_4$. However, there is still room for discussion due to the heterogeneity in methods (dosage and duration of treatment), results, and tertiary outcomes, as well as the small number of studies found with respect to this important issue.

Keywords: Magnesium Sulfate ($MgSO_4$); Postpartum Hemorrhage (PPH)

1. INTRODUCTION

In high resource countries we see an increase in Postpartum Hemorrhage (PPH) during the last decade [1,2]. We suspect a correlation with magnesium sulfate ($MgSO_4$) because of three following effects.

Firstly, magnesium sulfate is widely used in obstetrical care for the prevention of eclampsia during pregnancy, although the exact pharmacological mechanism of $MgSO_4$ in preventing eclampsia is not known [3]. Cerebral vasoconstriction has been reported in women with eclampsia [4]. Magnesium sulfate vasodilates intracranial vessels distal to the middle cerebral artery and hence may exert a main effect in the prophylaxis and treatment of eclampsia by relieving cerebral ischemia. Furthermore, $MgSO_4$ is effective as an antihypertensive drug. This antihypertensive effect is also explained by vasodilatation [5]. Vasodilatation could induce PPH.

Secondly, $MgSO_4$ can be applied as a tocolytic drug. Magnesium maintenance therapy is a type of tocolytic therapy used after an episode of preterm labour in an attempt to prevent the onset of further preterm contractions [6]. Therefore, atonia or hypotonia of the uterus could be possible when using magnesium sulfate. Uterus atonia is the most common cause of postpartum hemorrhage (PPH) [7].

Thirdly, there are several effects of magnesium sulfate reported on blood. Although results are conflicting, side effects are described. Several authors find a significant increased bleeding time in preeclamptic patients treated with $MgSO_4$, [8-10] while another author did not find a difference in bleeding time in healthy volunteers given $MgSO_4$ [11]. Furthermore, significantly inhibited platelet aggregation [10] and an increased RBC-deformability in a 24 hour intravenous magnesium therapy are mentioned [12].

In 1964 authors already had the impression that the observed external blood loss, during and soon after, delivery was excessive when using $MgSO_4$. However they did not show proof [13]. In the latest Cochrane review conflicting results are reported [14]. When comparing $MgSO_4$ with placebo, no significant difference in PPH is found. However, when comparing $MgSO_4$ with Nimodipine (calcium channel blocker), a significant increase in PPH is found. An explanation for these differences is

not given.

In summary, magnesium sulfate may induce vasodilation, tocolytic effects, and effects on blood (*i.e*. red cell deformity, inhibited platelet activity and prolonged bleeding time). If the risk of PPH is increased in women treated with $MgSO_4$ one should be more aware and prepared for obstetric blood loss. Therefore, we performed a systematic review of the literature to analyze whether $MgSO_4$ treatment increases the risk of PPH.

2. MATERIALS AND METHODS

We created two queries for the database "Pubmed." The elements of our question are "Magnesium sulphate" and "PPH." We compiled a query with synonyms. Synonyms were connected with "OR" in the search string while the intervention ($MgSO_4$) and outcome (PPH) were connected with "AND." Using this procedure we found 234 hits. We screened the titles and abstracts and excluded non relevant articles, case reports and articles in other languages than English, German and Dutch. We only included Randomized Controlled Trials (RCTs) involving $MgSO_4$ treatment which gave original data about PPH. Of the three remaining articles [13,15,16] one met our inclusion criteria and was therefore included in this systematic review [15].

We assumed that in some randomised controlled trials concerning $MgSO_4$ in preeclampsia the incidence of PPH has been examined, but not mentioned in the abstract. Therefore, we searched with another search string for RCTs with $MgSO_4$ in preeclampsia treatment. With this procedure we found 28 hits wherein 7 possible relevant trials [15-21]. After reading these articles full text, 2 studies remained [15,17]. On screening references, 3 additional articles were found [22-24] of which one was relevant [22].

Furthermore, we searched in the Cochrane Library for PPH studies as well as solitary $MgSO_4$ studies. We found the three articles we already included [15,17,22] but also two additional relevant articles in which $MgSO_4$ was given for neonatal neuroprotection before preterm birth. [25,26]. However, one [26] gave no clear definition of PPH and was therefore not included after reading full text. So, eventually a total of 4 RCTs were included in our review (see **Figure 1** Flow chart).

Within the patient populations described in these articles [15,17,22,25] we selected the women of whom there was information about PPH, mostly women who were followed and treated during labour.

Some authors calculated the relative risk of PPH in women treated with $MgSO_4$ [15,17,25]. For the remaining article we calculated (using the information provided) the relative risk of the incidence of PPH and the 95% confidence interval.

Finally, we calculated a relative risk and the 95% confidence interval of the combined studies.

3. RESULTS

In **Table 1** the primary results of the trials are shown. The Magpie trial [22] included by far the most patients (10.141). Heterogeneity between the included studies has been found when comparing the primary outcome measurements *i.e*. eclampsia, duration of labour, disease progression and neuroprotection of the infant as well as the comparison *i.e*. placebo or Nimodipine.

Information on PPH was given on a total of 11,621 women. The results with respect to the incidence of PPH differ in the various articles (**Table 2**). The researchers of the Magpie trial [22] and Crowther *et al*. [25] did not found a significant change in the incidence of PPH in women when treated with $MgSO_4$.

Belfort *et al*. [17] however, do find a significant difference. PPH occurs in 2.4% of the women treated with $MgSO_4$ versus 1.0% of women in the control group (RR 2.4695%CI 1.09 - 5.56; p = 0.03.)

Witlin *et al*. [15] report a fourfold greater incidence of PPH in the $MgSO_4$ group, although this finding is not significant. There was a significant difference in the maximum dose of oxytocin used with Magnesium sulphate versus placebo (p = 0.036).

The calculated overall relative risk does not show an increase of the risk of PPH when using $MgSO_4$ (RR 0.964 (95%CI 0.886 - 1.050)).

4. DISCUSSION

In this systematic review we do not find a significant increase in PPH in women treated with $MgSO_4$.

Still, there are some interesting remarks to make. Two of four articles in this systematic review report a trend [15] or a significant difference in PPH [17]. However, the data given by the Magpie trial (with no significant difference) overrule all other results because of the large patient population. PPH was one of the many secondary outcome measures of this study. We wonder if we can draw any conclusions yet. Moreover, because the lowest dose of $MgSO_4$ was used in the two studies which showed no significant increased risk of PPH, including the Magpie study. They treated with 4 gram loading dose continued with 1 gram per hour for 24 hours at most. Belfort *et al*., who do find a significant difference, used the longest duration of $MgSO_4$ treatment. They treat with a maximum of 24 hours (mean 8.8 hour) during labour and always 24 hours post partum. This could explain the differences in outcomes, and thus the effects of $MgSO_4$. The dosage of $MgSO_4$ might be crucial in the risk of PPH. It could be possible that the dosage given in the Magpie trial is safe but that there is a threshold to provoke PPH.

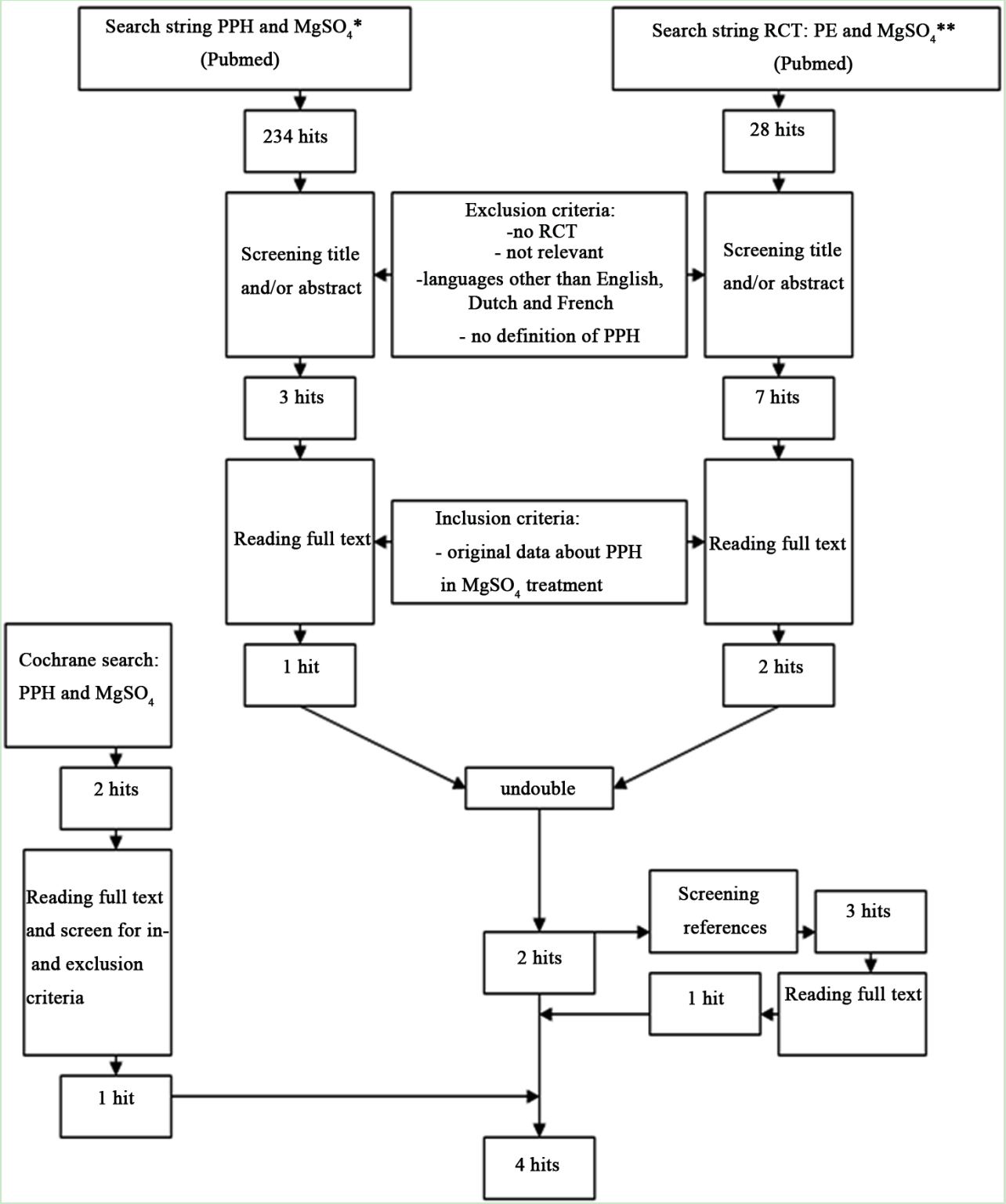

Figure 1. Flow chart of the Literature search, *search string: (((“Post partum” OR “Post labour” OR “Post delivery” OR “Pueperal” OR “Uterine”) AND (“Hypotonia” OR “Hemorrhagic” OR “Hemorrhage” OR “Heamorrhage” OR “Bleeding” OR “Bleed” OR “Blood loss”)) OR “Hypotonia” OR “Hemorrhage” OR “Heamorrhage” OR “Bleeding” OR “Blood loss”) AND (“Magnesium sulphate” OR “Magnesium sulfate” OR “$MgSO_4$” OR “Magnesiumsulphate” OR “Magnesiumsulfate”)) (August 2010). **Search string: ((“PE” OR “preeclampsia”) AND (“Magnesium sulphate” OR “Magnesium sulfate” OR “$MgSO_4$” OR “Magnesiumsulphate” OR “Magnesiumsulfate”)) AND limit [RCT] (August 2010).

Table 1. Primary results.

al.	(1996 - 200	Gynaecology		W wi yo 30 ag pla wi	eeclampsia		RCT	ed	And placebo	eclampsia With $MgSO_4$	
udy	Year of Publicatio (Year of Scanning	JAMA	1062	0)	ild eeclampsia	Duration of labour	Blind RCT	nded	Nimodipine and $MgSO_4$	Sig. more eclampsia with Nimodipine (especially post partum)	40/5055 (0.8%) vs 96/5055 (1.9%)	0.42 (0.29 - 0.60) p < 0.0001
agpie al	2002 (1998 - 200	Journal	No of patients	In	omen pregnant th fetus(es) unger than weeks gestational e if birth was anned or expected thin 24 hours	Peadiatric mortality and morbidity	Blind RCT	ed	$MgSO_4$ and placebo	$MgSO_4$ has no influence on the duration of labour	21/819 (2.6%) vs 7/831 (0.8%)	3.2 (1.1 - 9.1) p = 0.01
elfort al.	2003 (1995 - 200	Lancet	10141	1) M se pr							Median 17.8 hours (n = 67) vs 16.5 hours (n = 68)	p = 0.7
itlin al.	1997 (1995 - 199	New England Journal of Medicine	1650	0) Se pr	clusion	Primary outcome	Stud desig	ed	$MgSO_4$ And placebo	No significant differences in pediatric mortality; Less substantial pediatric motor dysfunction in the $MgSO_4$ group	87/629 (13.8%) vs 107/626 (17.1%) 18/533 (3.4%) vs 34/514 (6.6%)	0.83 (0.64 - 1.09) 0.51 (0.29 - 0.91)
owther	2003	American Journal of Obstetrics And	135	6) M pr	ild and vere eeclampsia	Eclampsia	Blind RCT	y tn	Comparison	Results		
					vere	Eclampsia	Not blir		$MgSO_4$	Sig. less		

Table 2. PPH in $MgSO_4$ treatment.

gpie trial	8774			ontrol group)	RR	p-value	$MgSO_4$ dose	$MgSO_4$ treatment time
lfort al.	1650	> 500 mL	750/4415 (17%)	774/4 359 (18%)	0.96 (95%CI 0.87 - 1.05)	NS	4 g loading dose followed by 1g/h	Maximum of 24h
tlin al.	135	> 500 mL after vaginal delivery and >1000 mL after caesarean section	20/831 (2.4%)	8/81 9 (1.0%)	2.46 (95%CI 1.09 - 5.56)	p= 0.03	6-g loading dose followed by 2 g/h or 4-g loading dose followed by 1g/h	Max. 24h antepartum (mean 8.8) and always 24h post partum
owther al.	1062	500 mL after vaginal delivery and >1000 mL after caesarean section	4/67 (6%)	1/6 8 (1%)	4.1 (95%CI 0.5 - 35.4)	NS	6-g loading dose followed by 2g/h	Until 12h post partum
l studies	11621	Primary PPH >600 mL	86/535 (16.1%)	99/52 7 (18.8%)	0.86 (95%CI 0.66 - 1.11)	P = 0.24	4-g loading dose followed by 1g/h	Until birth or up to 24 hours
udy	Patients	Major PPH >1000 mL	26/535 (4.9%)	25/5 27 (4.7%)	1.02 (95%CI 0.60 - 1.75)	P = 0.93		
			886/5848 (15.2%)	907/57 73 (15.7%)	0.964 (95%CI 0.886 - 1.050)	NS		
		Definition HPP	PPH ($MgSO_4$)	PPH (c				

Particularly, Witlin *et al*. report a significantly higher dosage of oxytocin needed in the $MgSO_4$ group (p = 0.036). This may suggest that a possible effect of $MgSO_4$ can be a hypotonic uterus.

Although we had to exclude the study of Friedman *et al*. [21] because the authors did not give numbers about PPH and therefore did not meet our inclusion criteria, there are some remarkable results. The authors examined side effects of $MgSO_4$ compared to phenytoin. They found a significant greater haematocrit fall after delivery when using $MgSO_4$ (7.6% vs. 4.7% (p = 0.0034)), as well as a significant greater blood loss (606 ml vs. 418 ml (p = 0.04)).

We do not question the proven and great value of $MgSO_4$ in preventing eclampsia or the indication when to start this treatment. But one can doubt the evidence about side effects. One may suggest that since 2002 $MgSO_4$ treatment possibly becomes more and more common. A false sense of security in preventing eclampsia could enhance the use of $MgSO_4$ and the duration of treatment. Remarkably, in this systematic review we found only very few articles (4) that studied PPH in combination with $MgSO_4$ treatment, while knowing that $MgSO_4$ is extensively used all over the world and PPH is a dangerous and frequent complication of labour [2].

It would be interesting to know the exact pharmacological effect of $MgSO_4$. This would help us to understand the function of $MgSO_4$ in preventing eclampsia as well as other possible side effects such as PPH. Theoretically, $MgSO_4$ still could influence the uterus tonus, the bleeding time and provoke vasodilatation.

To give a definitive answer on our question, ideally a trial with PPH as a primary outcome should be performed. Secondary, dosage and duration of $MgSO_4$ therapy should be considered, together with interventions to prevent PPH, *i.e*. the dosage of oxytocin. With respect to PPH, the decrease in haemoglobin or haematocrit could provide objective results. In women with HELLP syndrome the risk of PPH in combination with a possible trombopenia should be considered.

A limitation of our study is that we mainly systematically searched the Pubmed database. However, a screening in Embase did not show any relevant articles. Another limitation of our overview could be the heterogeneity of the articles included. We decided to only use an assessment for statistical heterogeneity with population size. One could question if you can compare women with preeclampsia with women with threatened preterm birth who are given $MgSO_4$ as neuroprotection for the foetus. However, we decided that when researching the unknown effect of $MgSO_4$ on PPH the indication for treatment are less relevant. Moreover, this heterogeneity is an argument for more and specific research.

In this systematic review, we do not find a significant risk of PPH when treating with $MgSO_4$. $MgSO_4$ has a great, important and proven role in the prevention of eclampsia. However, in our opinion, consensus on the question whether $MgSO_4$ does or does not influence blood loss during delivery is not possible, due to few and non specific studies and the heterogeneity of the relevant studies.

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