Oral magnesium supplements decrease high blood pressure (SBP > 155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis

Andrea Rosanoff, Michael R. Plesset

Center for Magnesium Education & Research, 13-1255 Malama St., Pahoa, HI 96778 USA

Correspondence: Andrea Rosanoff, Center for Magnesium Education & Research, 13-1255 Malama St., Pahoa, HI 96778 USA

<ARosanoff@gmail.com>

Abstract. Previously, we examined 44 human studies involving oral magnesium (Mg) supplementation for hypertension (HT), sorting them according to HT status, Mg dose and anti-hypertensive medication usage. We found that while some studies reported a significant lowering of blood pressure with Mg supplementation, others did not. We present here our first meta-analysis of a uniform subset from this series of studies.

Seven studies, involving 135 hypertensive subjects on anti-hypertensive medication continuously for at least six months, with no more than a two-week washout and with a mean starting systolic blood pressure (SBP) >155 mmHg, demonstrated a mean change of -18.7 mmHg [95% CI = -14.95 to -22.45] $p<0.0001$ and an effect size test (Cohen's d) = 1.19, i.e. a large and highly significant effect. Meta-analysis of diastolic blood pressure (DBP) for these same seven studies showed a mean change in DBP of -10.9 mmHg [95% CI = -8.73 to -13.1], $p<0.0001$, with an effect size test (Cohen's d) = 1.19.

Other studies from our original collection, approaching, but not meeting the >155 mmHg starting SBP values or not complying as regards anti-hypertensive medication usage, showed mean changes in both SBP and DBP with oral Mg that, while not approaching the high-responder values of the present study, appeared to include some high-responder subjects combined with low- or non-responder subjects.

This uniform subset of seven studies showed a strong effect of Mg treatment in hypertension, which is in stark contrast to results of three other meta-analyses. Using non-uniform sets of studies, the small effects reported in previous meta-analyses may reflect a blending of dissimilar studies, which acted to seriously underestimate the potential of Mg in hypertension in some (but not all) subjects. Within studies, blending of non-, moderate and highresponder subjects in any one study might mask strong effects of Mg treatment in some subjects.

Key words: hypertension, meta-analysis, oral magnesium treatment

doi:10.1684/mrh.2013.0343

Over 30 years ago, Turlapaty & Altura [1] reported that a low magnesium (Mg) medium caused contraction of blood vessels *in vitro*, and that addition of Mg to the medium resulted in a relaxing of these isolated arterial vessels. In the intervening years, a strong basis for Mg as an important factor in blood pressure homeostasis has been established [2], although several human studies measuring the effect of Mg supplements on hypertension have shown widely varying

To cite this article: Rosanoff A, Plesset MR. Oral magnesium supplements decrease high blood pressure (SBP > 155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis. *Magnes Res* 2013; 26(3): 93-9 doi:10.1684/mrh.2013.0343

results [3]. As suboptimal Mg intake has become widespread [4,5], fully exploring Mg supplementation as a possible treatment for high blood pressure deserves attention, as treatment of this growing and most important risk factor for cardiovascular disease has become a priority of Western medicine.

Since 2000, three meta-analyses have been conducted. These have shown that of the various sets of the many human studies included, all have demonstrated little or no change in blood pressure with Mg [6-8], rather negating the general acceptance of Mg supplementation as a viable therapy for high blood pressure (BP) even though some studies have shown quite promising results [9]. Previously, our research center collected and sorted a comprehensive set of studies, qualitatively rather than quantitatively, according to daily Mg dose, normotensive *versus* hypertensive status of subjects at baseline, plus use or non-use of anti-hypertensive medications [3]. We found subgroups of studies that differed in their BP response to Mg supplements, suggesting that the meta-analyses already performed might have diluted their results by inclusion of studies from these various, non-homogeneous subsets [3]. If so, oral Mg supplements may effectively lower both SDB and DBP significantly in some, but not all studies, and in some but not all subjects. Targeted meta-analyses of existing studies may tell us more about which study/subject parameters effectively responded to oral Mg supplementation regimes and which did not. Within this qualitatively sorted set of studies, we observed a subgroup of Mg-treated hypertensive studies with an initial SBP above a certain level that were all high-responder studies; we have consequently meta-analyzed this group of studies.

Methods

From a categorized list of 44 human, Mg-for-hypertension studies collected by us [3] and/or referenced in other reviews and meta-analyses [6-8], we noticed that a particular subset of studies (study subjects using anti-hypertensive medications for at least six months with no more than a two-week washout period), with an initial mean SBP above a certain figure (supine or sitting SBP>155 mmHg), all showed a very high response to oral Mg therapy. We quantified this observation by combining them in a meta-analysis and analyzed what was similar about these studies as well as how they differed from other similar, but non-high-responder studies.

Mean differences between final and baseline blood pressure values for both SBP and DBP from seven, high-responder studies (*table 1*) were weighted by $1/sem^2$ and combined in meta-analysis using a fixed-effects model to estimate an overall pooled, weighted mean difference and its 95% confidence interval. Effect size was quantified using Cohen's d calculation; heterogeneity between trials was assessed using the I^2 index.

Results (*figure 1*)

Change in blood pressure

Seven studies involving 135 hypertensive subjects with a mean starting systolic blood pressure (SBP) >155 mmHg, showed a mean change in SBP of -18.7 mmHg [95% CI = -14.95 to -22.45] $p<0.0001$ and a mean change in DBP of -10.9 mmHg [95% CI = -8.73 to -13.11], $p<0.0001$.

High effect size

The effect size test for changes in SBP with Mg supplements showed Cohen's d = 1.19, i.e. a very highly significant effect, and for changes in DBP, a similarly high effect size according to Cohen's d = 1.19. To put these d values into perspective, interpretation of this value is as follows: 0.2-0.3 = low effect, 0.5 = medium, 0.8 = high effect.

Heterogeneity measurements

Heterogeneity measurements for SBP showed a high degree of homogeneity, i.e. $I^2 = 0\%$. Heterogeneity calculations for DBP showed $I^2 = 68\%$, a high degree of heterogeneity due to the low variance in one study's reported DBP: although consistent in effect with the rest of the high-responder studies. Sebekova *et al.* [12] reports an unusually low variance for their initial and final DBP, less than half the variance on a percentage basis than that for SBP measured in the same 12 subjects, as well as a DBP variance result far lower than that seen in the other six studies. (See *table 1* and discussion below).

Table 1. Details of each study in the meta-analysis

Citation [Ref]	N	Mg daily dose (form of Mg)	Time on Mg (wks)	Anti-HT medication	Starting mean DBP mmHg (SD)	Ending mean DBP mmHg (SD)	Starting mean SBP mmHg (SD)	Ending mean SBP mmHg (SD)
Michon, 2002 [9]	20	13.3 mmol (Slow-Mag B6)	6	Ace inhibitors	94.8 (7.80)	85.0 (9.60)	162.1 (14.10)	141.2 (11.40)
"	18	"	"	Beta-blockers	94.2 (7.90)	88.10 (5.50)	155.3 (14.90)	136.7 (9.50)
"	18	"	"	Ca-channel blockers	90.3 (8.50)	84.70 (6.10)	162.2 (14.10)	142.2 (7.90)
"	18	"	"	Diuretics	93.9 (5.90)	86.70 (8.20)	157.6 (12.30)	141.7 (10.30)
Paolisso *et al.*, 1992 [8]	9	15.8 mmol (Mg pidolate)	8	Diuretics	96.0 (12.0)	89.0 (15.0)	173 (27.0)	159 (12.0)
Guerrero-Romero & Rodriguez-Moran, 2009 [10]	40	18.5 mmol ($MgCl_2$)	17	All subjects on anti-HT medications[a]	88.4 (14.50)	79.7 (7.10)	161.1 (26.0)	140.7 (11.9)
Sebekova *et al.*, 1992 [11]	12	10.5 mmol (dichloro-aspartate-HCl)	13	Ca-channel blockers[b]	95.83 (2.87)	81.76 (3.26)	161.67 (11.74)	140.42 (13.72)

[a] All subjects on anti-hypertensive medications for at least six months, personal communication from authors.
[b] All subjects on Ca channel blocker given a two-week washout before start of oral Mg therapy.

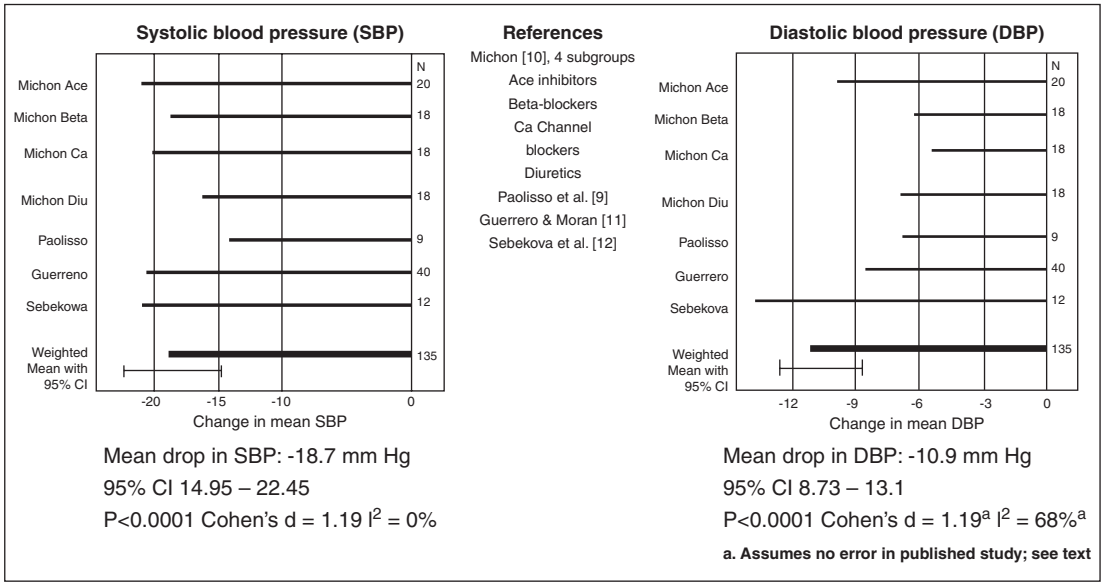

Figure 1. Changes in systolic and diastolic blood pressure associated with Mg supplementation in seven clinical trials.

Study similarities *(table 1)*

All seven high-responder studies showed a mean, baseline supine or sitting SBP>155 mmHg. It is possible that in all seven studies most or all subjects had been taking some form of anti-hypertensive medication for at least six months, however in the study by Sebekova *et al.* [12], it is likely, but not certain, that the subjects were on anti-hypertensive medications throughout the study after a two-week wash-out period (personal communication [24]).

Differences between the studies and similar non-high-responder studies

Two other studies, with a mean, baseline, supine SBP >155 mmHg, did not have high responders: Reyes *et al.* [13] and Sanjuliani *et al.* [14]. The first of these studies [13] was eliminated from the meta-analysis because of a very large placebo effect. Sanjuliani *et al.* [14], in a study involving 15 subjects with a mean baseline SBP of 158.8 mmHg, showed a mean change in SBP of only -7.6 mmHg, which was certainly not in same the range as that found in the seven high-responder studies. However, this study reported that 40% of subjects, i.e. n = 6, showed large changes in blood pressure, while the other 60%, n = 9, showed little, slightly positive or no change in blood pressure. Thus, the total change in SBP for all 15 subjects (-7.6 mmHg) × (15 subjects) = -114 mmHg was spread between only n = 6 subjects. These six subjects thus showed a change of -114/6 = -19 mmHg in their SBP, within the range of the high-responder studies. A similar calculation for DBP shows the mean change in DBP of -9.5 mmHg for six high responders, was again, quite similar to the high-responder studies in our meta-analysis. This blending of high and low, or no blood pressure response with Mg supplementation into an overall mean, obscured the 40% of high responders in the study by Sanjuliani *et al.* [14]. A similar blending of high, moderate and low or no response subjects into a final mean, with an overall low effect can be seen in other studies [15, 16]. We speculate that hypertensive subjects showing no response to Mg treatment might be essentially hypertensive, without any Mg deficit or imbalance and are, in fact, Mg replete [3, 17, 18]. Perhaps a potassium deficit [19], a sodium:potassium imbalance [20], a calcium imbalance [21, 22], or a calcium:magnesium imbalance, as exemplified in metabolic syndrome [22, 23], or some combination of these, not solely Mg-related causes essential hypertension could be producing the high blood pressure. Cases and studies where Mg treatment elicits only a moderately lowered response may involve patients with a combination of nutritional imbalances or deficits, and not just a deficit of Mg alone.

Discussion (*table 2*)

In contrast to the present study, previously published meta-analyses of Mg treatment for hypertension all found small reductions in BP with Mg supplementation that were possibly significant statistically, but too small in effect to be clinically relevant. How are such varying results to be explained?

Non-uniform studies in three previous meta-analyses

Quite possibly, the blending of dissimilar studies in the three previous meta-analyses diluted any effect of Mg supplementation on hypertension in their resulting conclusions. Mg supplement studies on normotensive subjects show no significant change in either SBP or DBP, even with Mg doses as high as 25 mmol/day [3, 15]. The previous three meta-analyses of Mg for hypertension largely missed this set of high-responder studies, while two included studies with subjects that were normotensive at baseline. Dickinson, *et al.*, 2006 [7] included only one of the high-responder studies [9] in their set of 12 clinical trials, and considered it an outlier, eliminating it from their *post hoc* analysis due to its "very different findings compared to the other trials" (see Dickinson *et al.* [7], p. 5). Jee *et al.* [6] did not include any of the high-responder studies and had six normotensive studies in their meta-analysis of 20 studies, which concluded that Mg supplementation resulted in only a small overall reduction in BP. The latest meta-analysis of Mg supplementation for hypertension, Kass *et al.*, 2012 [8], used two of the high-responder studies [9, 11] and seven normotensive studies in their meta-analysis of 23 studies, and concluded that Mg supplementation achieves a small, but clinically insignificant reduction in BP. Calculation of a simple mean from a collection of high-, moderate- and low- or no-response

Table 2. Comparison of four meta-analyses for effect of oral Mg treatment on blood pressure or hypertension

	Jee *et al.* [5]	**Dickinson *et al.* [6]**	**Kass *et al.* [7]**	**High responders (*figure 1*)**
Effect Size				
SBP (mmHg)	-0.6	-1.3	-3 to -4	-18.7
DBP (mmHg)	-0.8	-2.2	-2 to -3	-10.9
Hedges g:	NR	NR	0.32 – 0.36	NR
Cohen's d:	NR	NR	NR	1.19 SBP 1.19 DBP[a]
Heterogeneity	High (Cochran's Q)	I^2 = 62% SBP I^2 = 47% DBP	I^2 = 88% SBP I^2 = 82% DBP	I^2 = 0% SBP I^2 = 68% DBP[a]
Study details				
# of studies	20	12	23	7
# of Normotensive studies	6	1	7	0
# High responder studies	0	1	2	7
Total # subjects	1220	545	1173	135

[a] Based on assumption of no error in published study; see text.
NR = not reported; I^2 = heterogeneity by I^2 index

subjects could easily "hide" a set of high-responder subjects. The high responders of the Sanjuliani *et al.* [14] study were hidden in blended results that included low or non-responders (See Results above). A similar blending of high-, moderate- and low- or no-response subjects into a final mean with an overall low effect can be seen in other studies [15, 16], but most of these Mg for hypertension studies do not give individual results or discuss variations of response within the study. Meta-analysis that includes studies with "hidden" high responders and including studies on normotensive subjects could easily miss a subset of subjects with a significant blood pressure response to Mg supplementation and easily thus underestimate the great potential of oral Mg treatment for some hypertensive subjects.

A comment on the high heterogeneity of the DBP results

The effects of Mg on BP are in the same direction and of similar magnitude for all seven studies, hence the very good results for the t test and confidence limits. The high heterogeneity figure for DBP is a good example of the difference between the statistic and the usual, literal meaning of the word "homogeneity," meaning sameness or uniformity. The homogeneity statistic measures the likelihood that the various studies are different due only to expected statistical variation. The very low standard deviation (SD) for the baseline and final DBP figures in the Sebekova *et al.* [12] study, in comparison with SDs of the other studies makes statistical homogeneity appear unlikely (Personal Communication [24]).

These SDs seem odd, since they are proportionally so much smaller than those for SBP, presumably taken at the same time, and much smaller than those in all the other studies. It appears that there was possibly an error in calculating the SDs for DBP, however, given the very long time since the study was performed, the raw data are no longer available [24]. If these SDs are more like those for SBP in the study, and those in the other studies, the heterogeneity figure is zero, but to confirm that would require the original data. The effect size, Cohen's d, is larger with the smaller SDs; using those with the corrected SDs that we assumed, Cohen's d is smaller but still high, i.e. 0.95.

Conclusion

From a categorized, comprehensive list of Mg-treatment-for-HT studies, we found a category of high-responder studies, all with a mean, baseline,

supine or sitting SBP >155 mmHg. Meta-analysis of this set of seven studies shows a very strong effect of Mg treatment for hypertension (n = 135 subjects, lowering SBP by 19 mmHg and DBP by 11 mmHg), in stark contrast to the results of three, previously published meta-analyses. These three meta-analyses included few, if any, of these high-responder studies, but did include low- or non-responder studies of normotensive subjects, resulting in a blending of dissimilar studies that seriously underestimates the potential for Mg treatment for hypertension in some (but not all) subjects. Just from the numbers point of view, the large change effects that are seen in certain populations are diluted by the populations with lower baseline means. In addition to lowering the effect of Mg by blending dissimilar studies in a meta-analysis, blending of non-responder, moderate-responder and high- responder subjects in any one study's results may mask strong effects of Mg treatment in some subjects. A targeted approach using uniform sets of studies may provide more information about Mg treatment for essential hypertension, and might reveal evidence for the beneficial and appropriate use of Mg therapy in the treatment of hypertension. At any rate, to encourage more uniform results, human studies on oral Mg treatment for hypertension should limit their subjects to those who are:

- 1) hypertensive – do not include a mixture of hypertensive and normotensive subjects;
- 2) either taking anti-hypertensive medications or not rather than a combination;
- 3) either have a base-line SBP>155 mmHg or have a base-line SBP<155 mmHg rather than a combination of both.

Disclosure

Financial support: none. Conflict of interest: none.

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