# Magnesium Prophylaxis of Menstrual Migraine: Effects on Intracellular Magnesium

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## SYNOPSIS

**The effects of oral Magnesium (Mg) pyrrolidone carboxylic acid were evaluated in 20 patients affected by menstrual migraine, in a double-blind, placebo controlled study. After a two cycles run-in period, the treatment (360 mg/day of Mg or placebo) started on the 15th day of the cycle and continued till the next menses, for two months. Oral Mg was then supplemented in an open design for the next two months.**

**At the 2nd month, the Pain Total Index was decreased by both Placebo and Mg, with patients receiving active drug showing the lowest values (P<0.03). The number of days with headache was reduced only in the patients on active drug. Mg treatment also improved premenstrual complaints, as demonstrated by the significant reduction of Menstrual Distress Questionnaire (MDQ) scores. The reduction of PTI and MDQ scores was observed also at the 4th month of treatment, when Mg was supplemented in all the patients.**

**Intracellular $Mg^{++}$ levels in patients with menstrual migraine were reduced compared to controls. During oral Mg treatment, the $Mg^{++}$ content of Lymphocytes (LC) and Polymorphonucleated cells (PMN) significantly increased, while no changes in plasma or Red Blood Cells were found. An inverse correlation between PTI and $Mg^{++}$ content in PMN was demonstrated.**

**These data point to magnesium supplementation as a further means for menstrual migraine prophylaxis, and support the possibility that a lower migraine threshold could be related to magnesium deficiency.**

**Key words: Magnesium, menstrual migraine.**

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## INTRODUCTION

Several drugs have been proposed for the management of menstrual migraine (MM), a cyclical form of migraine headache particularly resistant to pharmacological treatment.[1] Among them, vaso-active substances,[2] non steroidal antiinflammatory drugs,[3] drugs acting on neurotransmitters,[4] hormones,[6] and so on, have been shown to be better than placebo. These different compounds are active both in the vascular and in the neural areas and their effects do not provide a basis for understanding the pathogenesis of MM.

MM is commonly associated with other symptoms of the late luteal phase, altogether defined as "premenstrual syndrome (PMS)".[6] Although the clinical features of MM are different from those of PMS,[7] it remains to be established how pre-menstrual depression, irritability, weight gain, etc. can condition the appearance of MM later on in the cycle. Furthermore, some neuroendocrine findings are shared by patients with both MM and PMS.[8]

Some years ago, Abraham[9] hypothesized that a magnesium (Mg) deficiency could account for many of the cyclical symptoms of PMS. Considering the modulation by Mg of neural excitability, plasma membrane stability and vascular contraction,[10] migraine could be included among these cyclical symptoms caused by Mg deficiency. Recently, Welch's group demonstrated reduction of intracellular Mg in the cortex of migraine patients during an attack.[11] Using another method we have demonstrated that PMS sufferers are characterized by a reduced content of Mg in lymphocytes, compared to asymptomatic controls.[12] Using an oral preparation of Mg (pyrrolidone carboxylic acid) we have now evaluated the effects of Mg supplementation upon MM patients, in a double-blind, randomized design versus placebo.

## MATERIALS AND METHODS

**Subjects and Protocol.** Twenty-four patients affected by perimenstrual migraine for 2-9 years participated in the study. Their ages ranged from 28 to 36 years (mean 30.3 yrs.). Patients noted that their symptoms frequently affected social interactions and working activity. Fifteen women (27.8 yrs) without any history of migraine or PMS served as controls. No concurrent diseases were present at entry into the study, kidney and hepatic functions being normal, Patients and controls reported normal menstrual cyclicity and none of them used oral contraceptives.

In the patients, the evaluation of migraine was based on the filling out of a daily headache diary; duration and intensity of attacks (PTI)[13] were recorded. The evaluation of premenstrual symptoms was based on the prospective filling out of the Moos

Menstrual Distress Questionnaire (MDQ)[14] for two consecutive menstrual cycles. After the two months run-in period, the patients wore randomly assigned to placebo (PL) or drug (MAG) for the next two cycles, in a double-blind design. In the following two cycles, both PL and MAG groups received the active drug. Magnesium pyrrolidone carboxylic acid (MAG 2, LIRCA-Synthelabo, Italy) or placebo wore administered three times a day, starting from the 15th day of the menstrual cycle till the next menstrual flow. The daily amount of magnesium was equal to 360 mg of $Mg^{++}$. Both the headache diary and the MDQ wore administered during the two run-in cycles, and at the 2nd and 4th cycles of treatment. Data from the run-in period wore averaged and served as reference basal value.

Blood samples for $Mg^{++}$ evaluation were taken before, and at the 2nd and 4th months of treatment at two separate times, i.e. the 20th and 25th days of the cycle. Four times (3 cases) the menses occurred before the 25th day of the cycle and only one blood sample was collected. Controls underwent the same blood sampling and only once the menses occurred before the 25th day of the cycle. The levels of $Mg^{++}$ then measured were averaged and one $Mg^{++}$ value for each menstrual cycle was considered.

Four patients dropped out from the study and data are therefore calculated on 20 MM patients. One woman became pregnant in the run-in period, and another one suddenly changed her address, The two remaining cases left the study because of side effects: one reported continuous headache (in the placebo group) and the other one reported diarrhea (in the MAG group).

Data reported as M±SD were analyzed using Student's t test for paired observations.

**Magnesium assays.** Twenty ml of venous blood were collected from each subject, and were used for plasma, erythrocyte and leukocytes separation. After centrifugation (2250 × g for 15 min at 4ºC) plasma samples were frozen at -40ºC before analysis. Packed erythrocytes (RBC) were washed two times by resuspending the cells in cold saline (9 g/l) and centrifuging them. For lymphocyte (LC) isolation, 15ml of blood were placed in an acid-citrate-dextran solution. The cell-rich supernatants were layered over a FicolI-Hipaque (Histopaque 1077, Sigma) discontinuous gradient, and centrifuged (800 × g for 30 min). All steps wore performed within 3 hours of blood collection. After discarding supernatants the mono-nuclear and polynuclear cells were dried at constant weight, and wet washed in nitric acid solution. Microscopic examination of the lymphocyte suspension showed a mononuclear percentage of 90% or greater for the cellular elements, whereas in the case of neutrophils the percentage was higher (97%). The cation contents in LC and PMN have been expressed per unit of dry weight. Further details are reported elsewhere.[12]

Data were analysed using multivariate analysis of variance considering time and treatment as sources of variance. Student's t test for paired observations was used when appropriate. The method of least squares was used when appropriate. The method of least squares was used for linear correlations.

## RESULTS

Both PTI and MDQ scores during treatment are reported in figure 1. At the 2nd month, PTI decreased

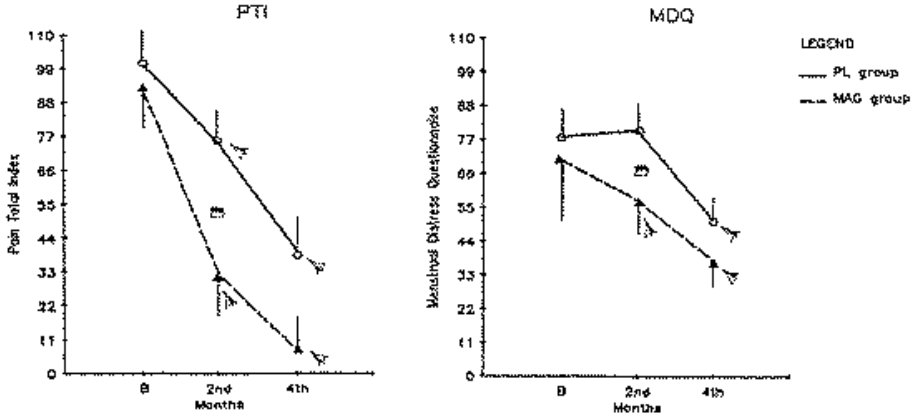


Fig 1.—Changes (M ± SD) of Pain Total Index and Menstrual Distress Questionnaire scores in patients treated with Magnesium (MAG; triangles and dotted line) or Placebo (PL; circles, solid line) for the first two months.
Arrows indicate a statistical significant change between 2nd month and basal values or between 4th and 2nd months values.
Symbols indicate a statistically significant difference between groups, at 2nd month of treatment, i.e. at the end of the double-blind study.

both in PL and MAG groups, these last patients reaching lower values (F=5.55, d.f. 1/19, P<0.03). The MDQ score, on the contrary, significantly decreased only in the MAG group (F=4.48, P<0.05). A further significant decrease was observed at the 4th month when both PL or MAG patients were given active treatment. The number of days with headache was significantly reduced by the treatment only in MAG group (from 4.7±3.1 to 2.4±2.2 at 2nd month, P<0.01).

In basal conditions, $Mg^{++}$ levels of patients were reduced compared to controls, in LC and PMN (Table 1).

**Table 1**
**Magnesium concentrations (M±SD) in controls and patients with menstrual migraine as evaluated in different intracellular and extracellular compartments.**

| | | Controls (15)º | Menstrual Migraine (20) |
|---|---|---|---|
| Plasma | (mcg%ml) | 20.8+2.0 | 21.5±2.1 |
| Red Blood Cells | (mcg%ml) | 40.7±6.5 | 39.9±6.1 |
| Lymphocytes | (mcg/g d.t.) | 997.9±177.1 | 753.9±146.5 |
| Polymorphonu-cleated cells | (mcg/g d.t.) | 746.5±140.4 | 557.0+125.4 |

ºNumber of cases P<0.01 vs controls

The $Mg^{++}$ content in the different compartments was similar among patients within the PL or the MAG groups. At the 2nd month of treatment, patients assigned to the MAG group showed a significant increase of $Mg^{++}$ in LC (from 721.4±130.2 to 858±128.5, p<0.005) and in PMN cells (from 562.4±140.1 to 666.5±180.4, p<0.04); while no changes were observed in plasma (from 20.9±1.5 to 21.6±2.1) and RBC (from 39.9±6.9 to 40.5±8.7). Patients given PL (placebo) did not show significant changes of the $Mg^{++}$ concentrations in any of the compartments. At the 4th month, however, in these patients too the $Mg^{++}$ levels in LC (from 730.6±144.8 at 2nd month to 815.7±149.7, p<0.05) and in PMN cells (from 540.5±169.9 to 672.0±178.5, p<0.05) were increased compared to the 2nd month's values.

An inverse correlation between PTI, and $Mg^{++}$ content in PMN, was found (r=-0.368, p<0.005) (fig. 2), while no relationships to MDQ were found.

## DISCUSSION

These findings demonstrate that MM patients have intracellular $Mg^{++}$ deficiency and indicate that oral magnesium supplementation improves perimenstrual migraine pari-passu with a restoration of the intracellular content of $Mg^{++}$. Magnesium supplementation, in the form of pyrrolidone carboxylic acid, has proven to be better than placebo, thus providing evidence for a specific pharmacological effect.

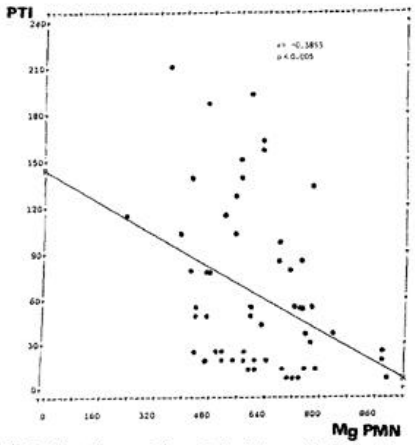


**Fig 2.—Negative correlation existing between the PTI and the $Mg^{++}$ content in Polymorphonucleated cells in the whole group of patients.**

The effect of placebo in these patients is well known and is confirmed in this study.[15] However, Mg treatment demonstrated an effect which was greater than placebo both at the 2nd and 4th months of observation. This conclusion is also supported by the fact that the number of days with headache was reduced only in patients treated with magnesium, and not in those on placebo.

The reduction of both the total MDQ score and the PTI observed with treatment indicate that MM is closely linked to PMS, at least in these patients. Indeed, a Mg deficiency in PMS patients has previously been found by us[12] and others[16] suggesting a common biochemical substrate for both conditions. The relief of perimenstrual migraine and pre-menstrual depression, produced by Mg treatment was concomitant with a definite increase in the $Mg^{++}$ content in both LC and PMN, i.e. two intracellular compartments that seem to be reliable markers of the magnesium balance in humans.[17] On the contrary plasma and RBC Mg levels were unaffected by the oral Mg supply.

A causal role of increased Mg concentration in the relief of perimenstrual migraine could be hypothesized since both groups of patients showed an immediate improvement of symptoms when the active drug was administered. Moreover, an inverse correlation between Mg levels in PMN, and PTI, supports the hypothesis reported above.

The possible role of a magnesium deficiency in migraine has been recently reported by Ramadan et al.[11] By using nuclear magnetic resonance spectroscopy they revealed a reduction of intracellular

$Mg^{++}$ content in the brain cortex of migraine patients during an attack. Previously, Jain et al.[18] found decreased Mg levels in the cerebrospinal fluid of migraine patients in respect to asymptomatic controls. Taking into account the protective effect against vasoconstrictor agents that magnesium exerts in artery and vein preparations,[19] the magnesium reduction demonstrated in migraine patients could have pathophysiological significance.

In conclusion, the present data point to magnesium supplementation as a further means for menstrual migraine prophylaxis, and support the possibility that a lower migraine threshold could be related to a magnesium deficiency.

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