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EFFECTIVENESS OF MAGNESIUM CITRATE ADJUNCTIVE THERAPY ON CRAMPING PAIN INTENSITY IN NOCTURNAL LEG CRAMPS PATIENTS AT BETHESDA HOSPITAL YOGYAKARTA

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ABSTRACT

Nocturnal Leg Cramps (NLC) are involuntary lower limb contractions that are painful and occur during long rest periods. Magnesium is thought to have potential in the treatment of NLC as one of the precipitating factors of NLC is low levels of certain minerals, such as magnesium deficiency. This study aimed to assess the effectiveness of magnesium adjunctive therapy in reducing cramping pain intensity in patients with NLC. This study was a randomized clinical trial, open-label, controlled group that was followed up for 2 weeks. 30 subjects who have been diagnosed with the NLC short-form adaptation of ICSD 2005 were divided into 2 groups; (1) the intervention group who was given standard NLC therapy (calcium and gabapentin) with additional therapy of magnesium citrate 100 mg (Hi-Mg100) one tablet a day, (2) the control group who was only given standard NLC therapy. NLC cramping pain was measured using the Numeric Rating Scale (NRS) before the administration of therapy (baseline) and at week 2 after therapy. The results obtained were the addition of magnesium to standard therapy provided a significant reduction in cramping pain intensity between before and after treatment based on the Wilcoxon signed rank test (p=0.000). However, there was no statistically significant difference effect between the two therapy groups based on the Mann-Whitney test (p=0.073). In conclusion, magnesium adjunctive therapy was not significantly more effective in reducing cramping pain than standard drug therapy in patients with NLC.

Keywords: Nocturnal leg cramps; NLC; Magnesium; Cramping pain; Pain intensity

1. INTRODUCTION

Nocturnal Leg Cramps (NLC) is defined as an involuntary painful contraction of the lower limbs that occurs for several seconds to minutes during prolonged periods of rest, particularly at night (Sebo et al., 2014). NLC often occurs in the gastrocnemius muscle, although it can also occur in the smaller muscles of the lower limbs (Buttaravoli, 2022). NLC can happen at any age but is most commonly seen in adults. According to the American Academy of Family Physicians (AAFP), the prevalence of NLC in adults is around 50-60%, while in children, it is approximately 7%. The prevalence of NLC tends to increase with age (Allen & Kirby, 2012).

The etiology of NLC, considered idiopathic, has led to a lack of effective therapy for its symptoms. In NLC, one possible precipitating factor is the low levels of certain minerals, such as magnesium deficiency. A magnesium deficiency can cause increased neuromuscular transmission and excessive excitation. Therefore, magnesium supplementation is considered beneficial as a therapy for NLC, considering that one of the precipitating factors of NLC is the low intracellular magnesium absorption (Maor et al., 2017; Sebo et al., 2014). Additionally, magnesium supplementation in the context of NLC therapy aims to be a curariform agent or an inducer of

muscle relaxation at the neuromuscular junction by inhibiting acetylcholine release from motor nerve terminals. The hope is to balance inhibitory and excitatory signals transmitted to the lower motor neuron, preventing nocturnal leg cramp symptoms (Liu et al., 2021).

Previous research on the benefits of magnesium for relieving NLC pain still needs to be more extensive and conclusive. Three randomized controlled trials (RCTs) conducted by Sebo et al. showed only slight differences between the effects of magnesium and a placebo on NLC prophylaxis. This means that magnesium is less effective as a therapy for NLC (Sebo et al., 2014). However, another study by Olha Barna et al. reported that magnesium had a significant effect in reducing the intensity of NLC pain, NLC symptoms and improving the sleep quality and quality of life of NLC patients (Barna et al., 2021). Based on the above research findings, the effectiveness of magnesium for NLC remains a matter of consideration, and this study aims to test the hypothesis that magnesium adjunctive therapy is effective in reducing cramping pain intensity in patients with nocturnal leg cramps. Moreover, this study is conducted as a reference for healthcare professionals to assess the improvement in NLC pain intensity in patients who receive magnesium supplements in the future.

2. METHODS

This research utilized the Open-Label Randomized Controlled Trial method. The study used primary data taken from the stroke center of Bethesda Hospital Yogyakarta, which included the intensity of pain values in NLC patients measured using the Numeric Rating Scale (NRS). The study was conducted for 2 weeks, from February 2023 to March 2023. The sampling was done using consecutive sampling, where subjects were diagnosed with NLC based on an adapted NLC short form from ICSD 2005. The subjects were divided into two treatment groups: the intervention group, which received standard NLC therapy (calcium and gabapentin) with an additional 100 mg of magnesium citrate therapy (Hi-Mg100) once a day, and the control group, which only received standard NLC therapy. Two visits were conducted, one before the therapy (baseline) and one in the second week. The primary data results will be analyzed using the Mann-Whitney test to assess the difference in mean NRS pain values between the intervention and control groups regarding effectiveness and the Wilcoxon signed-rank test to assess significant pain improvement within each group. The secondary results will be analyzed using the Spearman rank, Chi-square, and Fischer Exact tests. This study has obtained ethical clearance from the Ethics Committee of Bethesda Hospital Yogyakarta (No. 139/KEPK-RSB/XII/22).

3. RESULTS AND DISCUSSION

3.1. Subjects Characteristic

Of the 30 subjects, 17 were assigned to the intervention group, while 13 were assigned to the control group as shown in **Table 1**. The subjects in this study were predominantly female, with a total of 22 individuals (73.3%). It possibly due to the higher risk of NLC-related varicose veins in females than in males (Bahk et al., 2012; Hallegraeff et al., 2017). Furthermore, post-menopausal women are more likely to experience metabolic disorders, leading to poorer body homeostasis (Krishnan et al., 2018; Maor et al., 2017). We found a higher proportion of older or elderly patients, with 22 subjects (73.3%) aged ≥60 years and an average age of 65.17 ± 7.53 years. NLC predominantly affects individuals over 60 years old, indicating that neurological factors cause cramps. With age, motor and medullary neurons are lost, leading to more neuromuscular incoordination in the lower limbs than the upper limbs (Bordoni et al., 2022; Rabbitt et al., 2016).

In this study, 20 subjects (66.7%) reported that the duration of NLC cramps without treatment or only with massage was ≤ 10 minutes, which is consistent with previous research (Hallegraeff et al., 2017). The comorbid history found in the subjects was predominantly

neurodegenerative (96.7%) and hypertension (86.7%). In patients with degenerative lumbar disorders, they exhibited a lack of autoregulation feedback in regulating inhibitory inputs to alpha motor neurons, leading to hyperexcitability of motor units associated with NLC (Bordoni et al., 2022; Harmsen et al., 2021). Hypertension may be related to cramps through vascular decompression mechanisms, resulting in inadequate blood flow to the lower limb muscles, especially the quadriceps femoris muscle. Insufficient oxygen supply to these muscles can lead to higher levels of muscle spasms or cramps in hypertensive patients (Breda et al., 2014; Bufford W., 2016).

Table 1. Basic characteristics of research subjects

Variable	Magnesium 100 mg + Standard Therapy (n=17)	Standard Therapy (n = 13)	Total (n=30)	p-value (Chi-Square Analysis)
Age, mean ± SD (year)	65.76 ± 7.404	64.38 ± 7.922	65.17 ± 7.53	
<60 years	4 (23.5%)	4 (30.8%)	8 (26.7%)	0.657
≥60 years	13 (76.5%)	9 (69.2%)	22 (73.3%)	
Gender				
Man	2 (11.8%)	6 (46.2%)	8 (26.7%)	0.035
Woman	15 (88.2%)	7 (53.8%)	22 (73.3%)	
Smoking History				
Do not smoke	15 (88.2%)	7 (53.8%)	22 (73.3%)	0.035
Smoke	2 (11.8%)	6 (46.2%)	8 (26.7%)	
Comorbid				
Hypertension	13 (76.5%)	13 (100%)	26 (86.7%)	0.06
Diabetes mellitus	7 (41.2%)	3 (23.1%)	10 (33.3%)	0.297
Cardiovascular Disease	6 (35.3%)	5 (38.5%)	11 (36.7%)	0.858
Neurodegenerative	17 (100%)	12 (92.3%)	29 (96.7%)	0.245
Comedy				
Antihypertensive	13 (76.5%)	13 (100%)	26 (86.7%)	0.06
Antidiabetic	7 (41.2%)	3 (23.1%)	10 (33.3%)	0.297
Antiplatelet	6 (35.3%)	5 (38.5%)	11 (36.7%)	0.858
Neuroprotectant	17 (100%)	12 (92.3%)	29 (96.7%)	0.245
Cramp Duration (without treatment)				
≤ 10 minutes	10 (58.8%)	10 (76.9%)	20 (66.7%)	0.297
> 10 minutes	7 (41.2%)	3 (23.1%)	10 (33.3%)	

The predominant comedication in this study was neuroprotectants and antihypertensive agents. Neuroprotective agents such as vitamin E and B12 complex can be used as treatments for NLC (Allen & Kirby, 2012; Brown, 2015). In cases of NLC patients with a history of hypertension, hypertension treatment is also important in addressing vascular decompression issues, and certain antihypertensive medications, such as Calcium-channel blockers, may be required (Herzberg et al., 2017; Rabbitt et al., 2016).

Based on **Table 1**, it was found that the baseline characteristics of the subjects differed significantly between the two groups only in terms of gender and smoking history using Chi-square analysis (p = 0.035). The significant results could confuse the study because the differences in subject characteristics between the two groups cause baseline differences in terms of metabolic, physical, and mental characteristics. However, it was unavoidable that the prevalence of women suffering from NLC is higher than that of men because risk factors for NLC in women were found to be less elevated than in men. One of the risk factors associated with the incidence of NLC in women is venous varicose veins. The prevalence of venous varicose veins is more often found in women than men because most jobs in women require more standing than men and women also use more high heels (Bahk et al., 2012; Hallegraeff et al., 2017). NLC was found to be slightly increased in the female population also related to the cause of NLC, one of which is metabolic disorders, where it turns out that post-menopausal women experience more metabolic disorders

so that the homeostasis system in the body is worse. This can trigger an increase in the prevalence of NLC in post-menopausal women compared to men (Krishnan et al., 2018; Maor et al., 2017). Likewise, a significant result on smoking history was found in this study due to the difference in the proportion of men and women in the two groups. In fact, the prevalence of smokers was found to be higher in men than women in Indonesia. Cigarette consumption can cause reduced blood flow to the calf muscles, making it one of the risk factors for NLC (Abate et al., 2013; Ayuningtyas et al., 2021; Fritschi et al., 2013; Maor et al., 2017).

3.2. Normality Test of Variables

Based on **Table 2**, the data distribution results show that the intensity of pain variables, including pre-intervention, post-intervention, and the difference in pain intensity between pre-and post-intervention in the two groups, are not generally distributed with a p-value < 0.05. However, the age variable follows a normal distribution with a p-value > 0.05.

3.3. Comparison of Average Pain Intensity

Based on the analysis of pain intensity data using the Wilcoxon Signed Rank Test in **Table 3**, it was found that both therapies, the additional magnesium therapy (p^b = 0.000) and the standard drug therapy (p^b = 0.001), resulted in a significant reduction in cramp pain intensity between before and after the therapy. Additionally, it was found that there was no significant difference in the value of the difference in pain intensity between the two groups (p^a = 0.073) based on the Mann-Whitney test.

Table 2. Variable normality test

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistics	**df**	**Sig.**	**Statistics**	**df**	**Sig.**
Pre-intervention Pain Intensity	0.283	30	0.000	0.819	30	0.000
Post-intervention Pain Intensity	0.242	30	0.000	0.880	30	0.003
The difference in Pain Intensity Pre-post intervention	0.227	30	0.000	0.881	30	0.003
Age	0.111	30	0.200*	0.960	30	0.314*

Table 3. Comparison of average pain intensity

NRS Pain Level	Magnesium 100 mg + Standard Therapy (n=17)	Standard Therapy (n=13)	Total (n=30)	p^a-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Before therapy	57.06 ± 6.860	53.08 ± 6.304	55.33 ± 6.814	0.151
2 weeks after therapy	28.24 ± 11.851	30 ± 8.165	29 ± 10.289	0.481
p^b-value	0.000*	0.001*		
Pre-post therapy difference	28.82 ± 8.575	23.08 ± 8.549	26.33 ± 8.889	0.073

***p^a*: Comparison between the intervention and control groups (Mann-Whitney test)**
***p^b*: Intragroup comparison before and after intervention under the same conditions (Wilcoxon-signed rank test)**
***p-value statistically significant**

Figure 1 shows that there was a more pain intensity reduction in the magnesium supplemental therapy group when assessed subjectively (28.82 ± 8.575 vs 23.08 ± 8.549). In addition, there was also a significant difference in pain intensity between the two groups, both in pain intensity values before therapy (pa = 0.151) and 2 weeks after therapy (pa = 0.481).

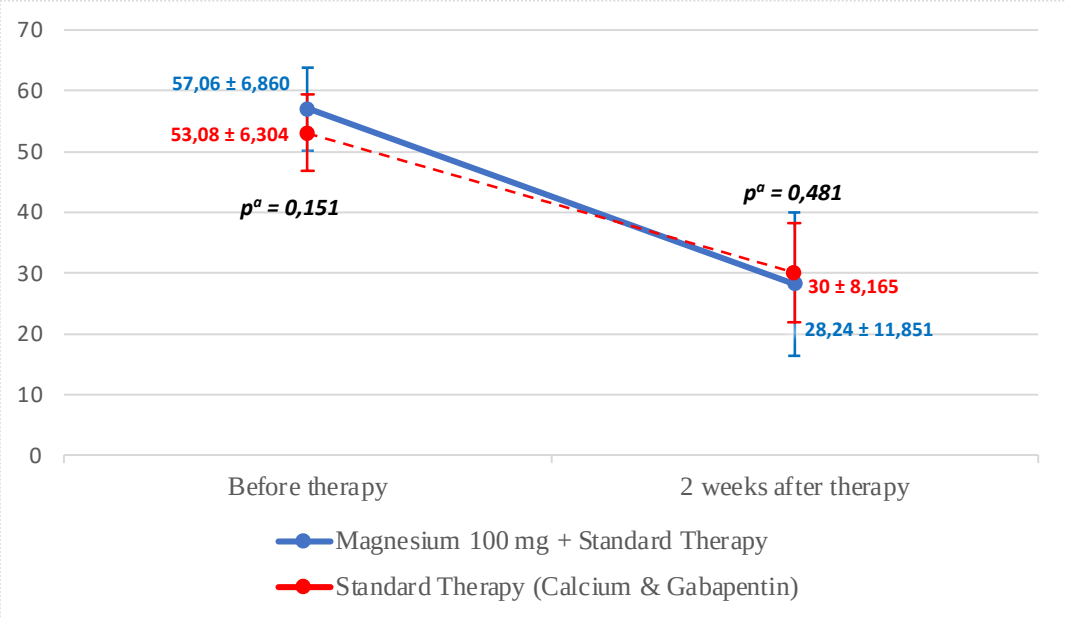

Figure 1. Graph of average NRS pain intensity

The level of improvement in subjective pain in **Table 4** was measured using the Subjective Global Assessment instrument at the end of therapy. The results showed a comparison of pain reduction: >50% reduction (5.9% vs 0%), 30-50% reduction (64.7% vs 61.5%), and a slight reduction of 10-30% (29.4% vs 38.5%). The Chi-square analysis obtained a p-value of 0.620, indicating no significant difference in the improvement of subjective pain intensity between the two groups. Based on the dose of drugs given, on average, previous studies gave higher doses of magnesium than the dose of magnesium in this study. In the previous studies, the doses of magnesium given was 226 mg and 300 mg per day (Barna et al., 2021; Supakatisant & Phupong, 2015). Meanwhile, in this study, 100 mg of magnesium was given every day. This proved that the possibility of a lack of daily doses of magnesium supplementation can affect the results of the effectiveness test. However, it should be noted that magnesium supplementation also has a maximum daily dose to avoid side effects that have been regulated in Tolerable Upper Intake Levels (UL), which for adults is a maximum of 350 mg daily outside of natural magnesium from food and beverages (Food and Drug Administration, 2016).

Table 4. Improvement of subjective pain intensity

SGA Pain Level	Magnesium 100 mg + Standard Therapy (n=17)	Standard Therapy (n=13)	Total (n=30)	P-value
	n(%)	n(%)	n(%)	
Pain is greatly reduced (>50%)	1 (5.9%)	0 (0%)	1 (3.3%)	0.620
Pain reduced (30-50%)	11 (64.7%)	8 (61.5%)	19 (63.3%)	
Slightly reduced pain (10-30%)	5 (29.4%)	5 (38.5%)	10 (33.3%)	

This study showed that the effectiveness of additional magnesium therapy in reducing or improving pain intensity is similar to standard drug therapy. These results are consistent with the study by Maor et al., (2017), where the effectiveness of magnesium supplementation on NLC severity was not significantly different from placebo, with a p-value of 0.38. This suggests that the etiology of cramps in NLC patients is not solely caused by intracellular magnesium deficiency but also by deficiencies in other mineral nutrients, such as calcium and sodium, which are involved in NLC cramp pathogenesis. Therefore, the potential of magnesium supplementation in addressing cramp intensity is likely to be low (Schwalfenberg & Genuis, 2017). One condition that leads to low intracellular magnesium levels due to magnesium depletion is pregnancy, where

the effectiveness of magnesium in reducing NLC severity is higher in this population (Sebo et al., 2014; Supakatisant & Phupong, 2015).

Additionally, the study by Garrison et al., (2011) explains that the effectiveness of magnesium itself depends on the formulation used and the characteristics of the population. This is related to magnesium's bioavailability and absorption rate, which decreases with age. In this study, an oral supplementation form with relatively low bioavailability was used, and the average age of the subjects was also geriatric (Garrison et al., 2011). In the study by Barna et al., (2021), a double-blinded RCT design was used to observe the effectiveness of monohydrate magnesium oxide on NLC episode frequency, duration, and induced pain compared to a placebo. The study was assessed during three visits: before therapy, 30 days, and 60 days after therapy. The effective results were only observed at 60 days after therapy, suggesting that the relatively short duration of treatment provided insignificant results regarding treatment effectiveness. Thus, the lack of significant results in the researcher's study could potentially be attributed to the relatively short treatment duration (< 8 weeks) (Barna et al., 2021).

In previous studies, the control group used a placebo group (Barna et al., 2021; Supakatisant & Phupong, 2015). This is different from the researcher's study, which involved an add-on approach. When using a placebo comparator, the effectiveness of test results obtained can be maximized as blinding can be performed on the intervention, and the test is single without the influence of other medications that may affect the effectiveness of test results. In the add-on group, biased effectiveness test results can occur, where standard drug therapy (gabapentin or calcium) may have a more dominant effect on pain intensity reduction (Castro, 2007; Laursen et al., 2020). Additionally, the average dose of magnesium given in previous studies was higher than the dose used in this study, which could also contribute to suboptimal test results (Barna et al., 2021; Supakatisant & Phupong, 2015).

3.4. Spearman Rank Test for Pain Intensity

Based on **Table 5**, the Spearman Rank test was conducted between age and pain intensity before therapy. The analysis revealed a p-value of 0.035 ($p < 0.05$) with a positive correlation coefficient (0.387). This result indicates a relationship between age and pain intensity before therapy, and the positive correlation suggests that as age increases, the initial pain intensity of the subjects also increases before undergoing therapy. Increased pain intensity with age is caused by increased psychological stress and a decreased pain tolerance threshold (González-Roldán et al., 2020; Yezierski, 2012).

Table 5. Spearman rank test for pain intensity

Variable		Pain Intensity NRS Score Before Therapy	Pain Intensity NRS Score After Therapy	Difference in NRS Scores Before and After Therapy
Age	Correlation coefficient	0.387	0.139	0.120
	Sig.	0.035*	0.465	0.528

In **Table 6**, Chi-square and Fischer Exact data analyses were performed to determine the relationship between gender and pain intensity. The results showed a significant association between gender and the difference in pain intensity before and after therapy, with a p-value of 0.047 ($p < 0.05$). These results show that males are more likely to experience a more considerable improvement in pain after therapy than females. Gender differences are associated with the pharmacokinetics and pharmacodynamics of consumed medications. Additionally, higher testosterone levels in males can result in a greater reduction in pain compared to females. Psychological stress is more prominent in females, and coping mechanisms also influence the level of pain reduction. Emotionally, males are expected to exhibit greater endurance and not show their pain (Khan et al., 2022; Madla et al., 2021; Templeton, 2020).

Table 6. Comparison of gender with pain intensity

Pain Intensity Before Therapy	Low (20 < x ≥ 40)	Currently (40 < x ≥ 60)	Tall (60 < x ≥ 80)	P-value
Gender				0.545
Man	0	8	0	
Woman	1	19	2	
Pain Intensity 2 Weeks Post-therapy	Very Low (≤20)	Low (20 < x ≥ 40)	Currently (40 < x ≥ 60)	*p.s*
Gender				0.369
Man	5	3	0	
Woman	8	12	2	
Difference in Pain Intensity Pre-Post Therapy	Very Low (≤20)		Low (20 < x ≥ 40)	*p.s*
Gender				0.047
Man	1		7	
Woman	12		10	

3.5. Medication Side Effects

Based on **Table 7**, it was found that there were medication side effects in 1 subject (5.9%) from the additional magnesium therapy group and 3 subjects (23.1%) from the standard drug therapy group. The reported side effects included drowsiness and mild nausea, which were considered mild and did not require hospitalization or specific treatment. The analysis found no significant difference in medication side effects between the two groups, with a p-value = 0.170.

The medication side effects in this study were mild and did not require any interventions. This demonstrates that in the management of neuropathic pain or cramp pain, gabapentin is an attractive therapy choice compared to other anticonvulsants because it causes mild and non-severe side effects (Seifollah et al., 2015). Additionally, mild side effects were found in oral magnesium therapy, with gastrointestinal symptoms such as diarrhea, nausea, vomiting, bloating, and constipation being the most commonly reported (Sebo et al., 2014).

Table 7. Comparison of the medication side effects between the 2 groups

Group	**Medication Side Effects**		**P-value**
	Yes	**No**	
Magnesium 100 mg + Standard Therapy (n=17)	1 (5.9%)	16 (94.1%)	0.170
Standard Therapy (n=13)	3 (23.1%)	10 (76.9%)	

This study has several limitations, such as the unblinding method during drug administration, which may have affected the results due to psychological factors, as patients were aware of their medications. Additionally, potential dose adjustments for magnesium were not analyzed and compared. Therefore, the optimal dose variation results could not be obtained. The duration of drug administration or intervention was also relatively short, which may explain why the significance of the results may have yet to be observed. Based on the limitations of this study, the researchers suggest that future studies use blinded methods and longer interventions with higher doses. Furthermore, it is recommended to increase the sample size to enhance the study's statistical power. Future studies are also advised not to solely focus on reducing pain scale but to consider overall aspects or total symptom score.

4. CONCLUSION

The administration of additional magnesium therapy with a supplementation dose of 100 mg daily for 2 weeks was not proven to be more effective in significantly reducing nocturnal leg cramp pain than a single standard drug therapy. Based on the results of this study, we couldn't

recommend the use of magnesium supplementation in short-term treatment yet. We might recommend the use of supplemental magnesium therapy when there are similar studies in the future with higher doses (>200 mg) and duration of treatment (>4 weeks) that prove magnesium to be effective.

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6. CONFLICT OF INTEREST

All authors declare no conflict of interest.

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