MEDICATION OVERUSE HEADACHE: THE EFFECTIVITY OF IV LIDOCAINE – MAGNESIUM

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English | https://doi.org/10.18071/isz.74.0323 | www.elitmed.hu

Background and purpose – The detoxification process in medication overuse headache is the most difficult process for the patient. We aimed to investigate the effectiveness of the combination of low dose IV lidocaine and magnesium (100 mg lidocaine and 1.25 mg magnesium) in patients with medication overuse headache during the detoxification process.
Methods – A total of 30 patients were included in the study; 15 received 24 hours of IV hydration, 15 received 1-hour lidocaine-magnesium infusion at the onset of pain in addition to the 24 hours of IV hydration. Headache severity (numeric rating scale, NRS), attack durations, onset of headache, monthly analgesic/triptan intakes, numbers of monthly headache days data were documented. We evaluated the severity of headache before and after daily treatment of two groups for one week.
Results – When both groups were compared, there was no significant difference in the pre-treatment NRS values, whereas, in the group receiving IV lidocaine-magnesium combination, there was a statistically significant decrease in the post-treatment NRS values in the first five days ($p < 0.05$).
Conclusion – An 1-hour combined infusion of lidocaine-magnesium may be considered as an alternative option for the patient to have a more quality detoxification process during the hospital stay, so that in parallel to the reduction in the use of multiple treatments (such as neuroleptics, benzodiazepines, antiemetics and opioids) and duration length of stay, the economic costs can also be reduced. The administration of combination will bring fewer side effects compared to their administration separately.

Keywords: *lidocaine, magnesium, headache, numeric rating scales, detoxification*

FÁJDALOMCSILLAPÍTÓ-TÚLHASZNÁLATHOZ TÁRSULÓ FEJFÁJÁS KEZELÉSE INTRAVÉNÁS LIDOKAINNAL ÉS MAGNÉZIUMMAL

Tepe N, MD; Tertemiz OF, MD
Ideggyogy Sz 2021;74(9–10):323–328.

Háttér és cél – A fájdalomcsillapító-túlhasználathoz társuló fejfájás kezelése során a detoxifikáció roppant kellemetlen a beteg számára. Vizsgálatunk célja az volt, hogy megállapítsuk az alacsony dózisú intravénás lidokain és magnézium (100 mg lidokain és 1,25 mg magnézium) kombinációjának hatékonyságát fájdalomcsillapító-túlhasználathoz társuló fejfájásban szenvedők detoxifikációjában.
Módszerek – Összesen 30 beteget vontunk be a vizsgálatba; 15 beteg 24 óra időtartamú intravénás hidratációban részesült, 15 beteg 24 óra időtartamú intravénás hidratáció mellett a fájdalom kezdetekor 1 órás időtartamú lidokain-magnézium infúziót is kapott. Dokumentáltuk a fejfájás súlyosságát (numerikus fájdalomskála, NRS), időtartamát, kezdetét, a havi fájdalomcsillapító-fogyasztást és a havi fejfájásos napok számát. Egy héten keresztül értékeltük a két csoport fejfájássúlyosságát a napi kezelés előtt és után.
Eredmények – A kezelés előtti NRS-értékekben nem volt szignifikáns különbség a két csoport között; az intravénás lidokain-magnézium infúziót kapó csoportban az első 5 nap során szignifikánsan csökkentek a kezelés utáni NRS-értékek ($p < 0,05$).
Következtetés – Az 1 órás időtartamú, kombinált lidokain-magnézium infúzió elősegítheti, hogy a fájdalomcsillapító-túlhasználathoz társuló fejfájásban szenvedők detoxifikációja sikeresebb legyen: csökkenjen a fájdalom és a gyógyszerhasználat (neuroleptikumok, benzodiazepinek, antiemetikumok és opioidok használata), továbbá csökkenjen a kórházi tartózkodás hossza, valamint költsége. A kombinált használat során kevesebb mellékhatás jelentkezik, mint akkor, ha a szereket külön-külön alkalmazzuk.

Kulcsszavak: *lidokain, magnézium, fejfájás, numerikus fájdalomskála, detoxifikáció*

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Érkezett: 2020. január 1. Elfogadva: 2021. február 28.

According to the 3rd edition of the International Headache Classification 2018, medication overuse headache is defined as a headache occurring on 15 or more days/ month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on ≥ 10 triptans/ ergotamine/opioids/combination analgesic medications/ combination of ergotamine, triptans, non-opioid analgesics and/or opioids or on ≥ 15 non-opioid analgesics days/month, depending on the medication) for more than three months[1]. Although its pathophysiology remains uncertain, central sensitization, intracranial hypersensitivity, dysfunction in descending pain modulation, hypometabolism in the anterior cingulate cortex, orbitofrontal cortex, insula and thalamus, and hypermetabolism in periaqueductal gray matter are among the abnormalities detected[2]. Although it develops on the basis of migraine most commonly, it is also observed in tension-type headache and cluster-type headache[3]. In medication overuse headache (MOH), there is significant labor loss and analgesic consumption, which brings economic disadvantages to the individual and the country. In a study conducted with 8 countries from Europe, the average annual cost per person for overuse of medication was found to be €3561[4]. A large part of MOH patients were former migraineurs who did not receive appropriate prophylaxis.

The detoxification (medication withdrawal) process is the basic approach adopted in this patient group, and then prophylaxis should be started according to the basic headache type. During detoxification, withdrawal symptoms lasting 2-10 days are observed following drug cessation; worsening of existing headache, nausea-vomiting, hypotension-tachycardia, sleep disturbances, restlessness, irritability may be observed[2]. Antiemetics, tranquilizers, neuroleptics, hydration (IV/oral) are recommended as treatment. The use of prednisolone (60 or 100 mg, 5 days) is controversial since it is not superior to placebo[5, 6]. Lidocaine is used as an acute treatment option for many types of headaches. There is no consensus in dosage, frequency, and the route of administration. Indications for the administration of lidocaine in headache include the control of pain in chronic daily headache (chronic migraine, tension-type headache, new daily persistent headache, and hemicrania continua), the withdrawal period of analgesic abuse, analgesic-induced rebound headache and treatment-resistant migraine headache. Although it is not included in the treatment guideline in reducing the treatment-resistant acute migraine headache, the administration of high-dose continuous lidocaine infusion (2-4 mg/kg) is included based on the literature data[7]. Magnesium sulfate (MgSO4) is a physiological antagonist of calcium ion in various ways. N-methyl-D-aspartate (NMDA) mediated ionotropic glutamate receptors have high permeability to Ca^{2+} and can be inhibited by Mg^{2+}. Many studies have found significantly reduced magnesium serum levels in migraine patients compared to control groups, while few have shown decreased levels especially in cerebro-spinal fluid[8, 9]. In the treatment of acute migraine attacks 1-2 g IV magnesium may be administered[10, 11].

In the literature there is no previous headache treatment study in which a combination of lidocaine and magnesium is administered. This study was carried out to assess the length of stay and pain response during the detoxification process in medication overuse headache patients. We aimed to investigate the effectiveness of the combination of low dose lidocaine - magnesium combination (100 mg lidocaine and 1.25 mg magnesium) in patients with medication overuse headache during the detoxification process in our hospital between 2018 and 2019.

Methods

STUDY DESIGN AND PARTICIPANTS

After the approval of the ethics committee of University Clinical Researches was obtained, patients who were admitted with the diagnosis of medication overuse headache in Balıkesir University Medical Faculty Neurology Service and were detoxified between 2018 - 2019 were screened retrospectively. A total of 30 patients were included in the study; 15 received 24 hours of IV hydration, 15 received lidocaine - magnesium infusion at the onset of pain in addition to 24 hours of IV hydration. During the one-week hospital stay, we documented numeric rating scales (NRS; 0-10) data to assess the severity of headache before and after treatment for those who received daily iv lidocaine-magnesium infusion and patients who received iv hydration for only 24 hours. We also documented the attack duration, onset of headache, monthly analgesic / triptan intake and monthly painful day data. Patients with chronic medication overuse headache between the ages of 18 and 65, patients who did not have previously received IV lidocaine and/or magnesium infusion, who did not have a history of heart disease, epilepsy, neuromuscular disease, allergy to lidocaine or magnesium, and who

Table 1. *Headache and demographic features of patients receiving IV hydration with IV lidocaine-magnesium combination (p<0.05)*

	Lidocain-magnesium infusion	Saline infusion	p-value
Age (year)	45±14.3	46±11.5	0.8
Weight (kg)	78.2±27	69.7±6	0.2
Height (cm)	157.9±24.3	165.5±6	0.2
NRS before treatment	8.9±0.4	9.2±1.3	0.3
Headache days/month	22.3±7	25.1±6.2	0.2
Monthly analgesic intake	50.3±32.6	81.7±72.7	0.1
Duration attacks	30±14.9	36.8±17.8	0.2
Headache duration (years)	16.7±10.4	18.7±7.2	0.5

did not use beta-blocker antiarrhythmic drugs were included. Patients with medication overuse headache who presented at our headache outpatient clinic were hospitalized and administrated an 1-hour infusion of 100 ml saline containing 100 mg lidocaine - 1.25 mg magnesium when they had pain in addition to IV hydration or only IV hydration. ECG (Electrocardiography), vital signs (systolic - diastolic blood pressure, heart rate, body temperature, respiratory rate), and basal NRS were checked in all patients before starting treatment. Patients who were administered IV lidocaine + magnesium infusion were monitored during the treatment and their vital signs were checked every 5 minutes for the first half hour and every 15 minutes for the last half hour.

STATISTICAL ANALYSIS

Comparison of NRS values by days, headache, and demographic features were performed using One-way ANOVA test. Results were taken as a mean ± standard deviation (SD). $P < 0.05$ was taken as the significance value.

Results

Data from fifteen patients who received IV hydration and IV lidocaine-magnesium when they had pain and fifteen patients who received only IV hydration, all of whom were followed up in our service for detoxification due to chronic medication overuse headache between 2018 and 2019 were obtained. Each group had three males and 12 females. The mean age was 45±14.3 in the group receiving IV lidocaine-magnesium, and it was 46±11.5 in the group receiving IV hydration. Basal NRS values were 8.9±0.4 in the IV lidocaine-magnesium group, while 9.2±1.3 in the group receiving IV hydration. The number of monthly painful days was 22.3±7 days in the IV lidocaine-magnesium group, and it was 25.1±6.2 days in the group receiving IV hydration. Monthly analgesic intake was 50.3±32.6 in the IV lidocaine-magnesium group, while it was 81.7±72.7 in the IV hydration group (p>0.05). The duration of the attacks was 30±14.9 hours in the IV lidocaine-magnesium group, and it was 36.8±17.8 hours in the IV hydration group (p>0.05). The duration of headache since headache onset was found to be 16.7±10.4 years in the IV lidocaine-magnesium group and 18.7±7.2 years in the group receiving IV hydration **(Table 1)**. When the pre-post-treatment NRS values were compared in the group receiving IV lidocaine-magnesium, a decrease was observed in the first four days, and

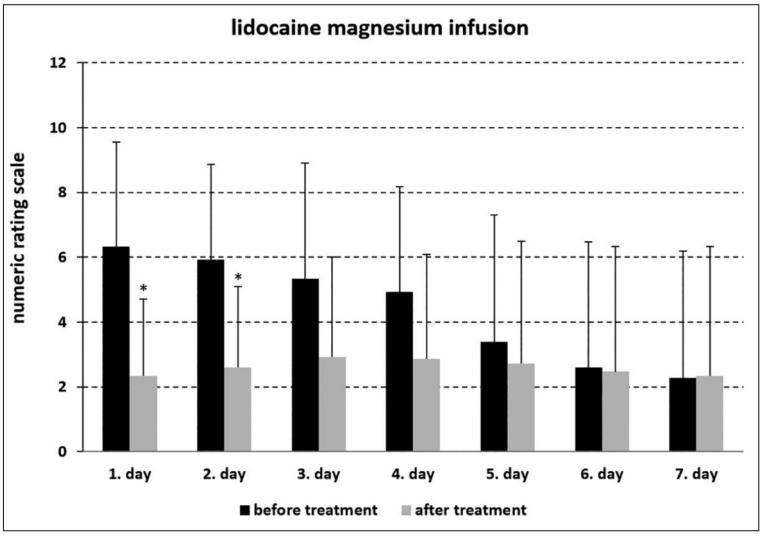

Figure 1. *Numeric rating scale values pre and post daily treatment in the group receiving IV lidocaine-magnesium (mean ± standard deviation). Although there was a decrease in NRS values after the treatment in the first four days, a statistically significant decrease was found only in the first two days*

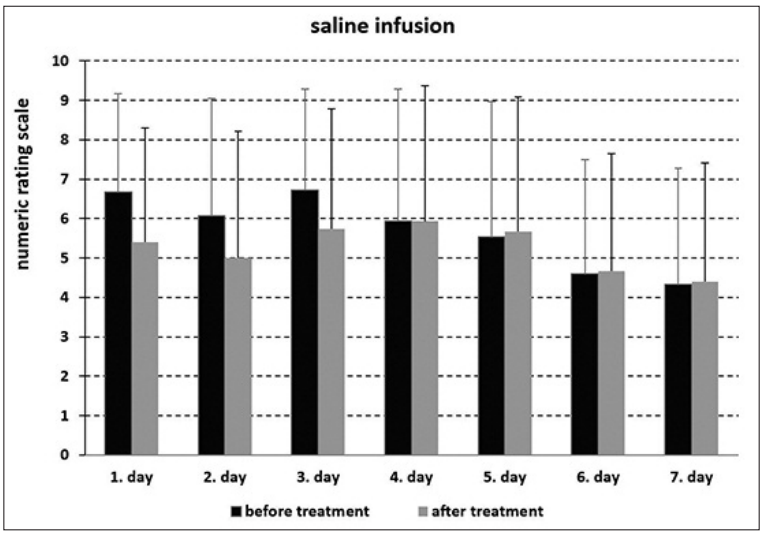

Figure 2. *Numeric rating scale values pre and post daily treatment in the group receiving IV hydration (mean ± standard deviation.). No significant difference was observed in the pre and post IV hydration NRS values during one week of treatment*

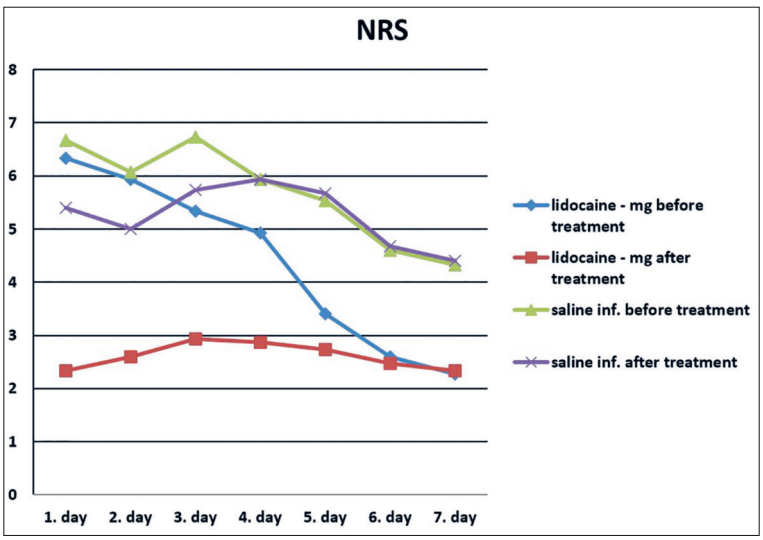

Figure 3. *Comparison of IV lidocaine-magnesium group with the only IV hydration group (mean ± standard deviation). In the first five days of treatment, a statistically significant decrease in NRS values was found in the group receiving IV lidocaine-magnesium, compared to the group receiving IV hydration*

this decrease was found significant in the first two days ($p < 0.05$) **(Figure 1)**. In the group receiving IV hydration, no significant difference was found in the pre-post-treatment NRS values during one week of treatment **(Figure 2)**. When both groups were compared lidocaine-magnesium treatment causes headache relief that is significant versus saline group and also significant in terms of pre-post treatment NRS values in the active group. Daily lidocaine-magnesium infusions cause a significant decrease in pre-treatment NRS values ($p < 0.05$) **(Figure 3).** When the daily NRS score changes between both groups were examined, it was found that there was a significant difference in the lidocaine-magnesium group in the first five days compared to the saline treatment group **(Figure 4).**

Discussion

The detoxification process for medication overuse headache involves a difficult process for the patient and the attending physician. In addition to increasing withdrawal symptoms, the severity of headache episodes increases, especially in the first week. The quality of life in these patients is impaired despite multiple medical treatments. Although the use of IV lidocaine or magnesium as a treatment option for acute migraine episodes is not included in the treatment guidelines, there are many studies on their effectiveness in the literature. However, there are no studies in which both are combined. Lidocaine infusions were administered as continuous infusions and under intensive care conditions; IV magnesium was administered to stop the episodes in the emergency service environment in patients who applied to emergency service[11, 12]. In this study, we administered low doses of lidocaine - magnesium combination (100 mg lidocaine and 1.25 mg magnesium, in the literature it is 2-4 mg/min lidocaine or 1-2 g magnesium) in one hour under monitorization in order to provide safety and patient comfort in the service. We found that low doses of lidocaine - magnesium administration were effective during the detoxification period in comparison with IV hydration. In addition, since high dose lidocaine needs to be followed up in the intensive care unit, it is troublesome in terms of patient comfort, requires strict monitoring of vital signs and it is an option with a high risk of side effects. No side effects were observed in any of the patients who received the combination. So we suggest that a low-dose lidocaine-magnesium combination is safe and does not need ICU monitoring.

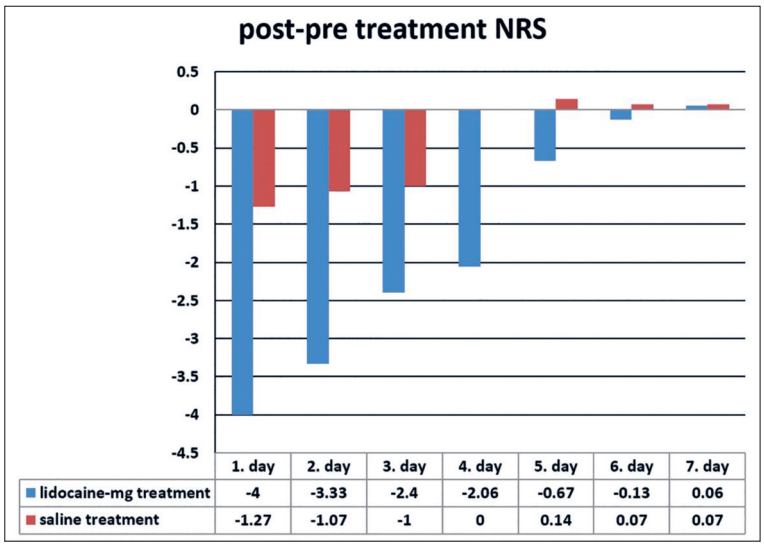

Figure 4. *Daily NRS difference between groups. A significant difference was found in the first five days in the lidocaine-magnesium group*

As it is known, during the first 30 minutes after IV lidocaine injection, lidocaine blood level decreases due to a half-life of 7-10 minutes, and the continuing infusion extends the half-life to 90-120 minutes[13]. In our study, it was found that post-treatment NRS values in the first five days statistically decreased in the combination therapy compared to the group receiving IV hydration. The effectiveness of the combination especially in the first five days, and then the decrease of the effectiveness with the decrease of NRS in the following days may be due to its effect on central sensitization in parallel with the episode severity in the first five days of the combination. In addition, the progressively statistically significant decrease in the daily pre-treatment NRS score starting from the first day of treatment supports the effectiveness of the combination. Possible analgesic action mechanisms of lidocaine results in a blockage in peripheral hyperalgesic effect and central hyperexitability due to the interaction with multiple Na channels, the interaction with different direct/indirect receptors and nociceptive transmission pathways (such as binding to muscarinic M3 receptors, inhibiting glycine receptors and causing the release of endogenous opioids). It has been suggested that prolonged lidocaine infusion resets central sensitization by modulating peripheral nociceptor dysfunction and/or intracranial hypersensitivity through sodium channels[14]. It has been stated that as an acute treatment option in patients with headache, lidocaine may be given at 2 mg/min (25mL/hr - 20-hour infusion) and a maximum of 4 mg/min without loading dose[15]. Common side effects include bradycardia, hypotension, vomiting, dizziness, headache, lightheadedness, numbness, paraesthesia, shivering, somnolence, tinnitus, blurred vision, diplopia, confusion, euphoria, nervousness; serious side effects are cardiac arrest, cardiac dysrhythmia, methemoglobinemia, loss of consciousness, seizure, tremor[13]. In a study lidocaine was started at 2mg/min as a 24-hour infusion for 7-14 days (average 8 days) in patients with chronic daily headache along with medication overuse headache, and it has been observed that the headache was gone at the time of discharge in 90% of the patients and this rate was 70% at six months[16]. In another study, treatment of patients with chronic daily headache were started with 1 mg/min of lidocaine and the dose was increased to 2 mg/min after 4 hours, with a maximum of 4 mg/min in some patients (mean 8.5 days). While the pre-treatment headache severity scale was mean 7.9, it decreased to 3.9 post-treatment[15]. Lidocaine alone was not determined to be superior to placebo when administered in short infusions for an average of 20 minutes (1 mg/kg)[12]. The short-term infusion alone may not have been effective due to the short half-life, but in the combination we have administered, the pain severity scale may decrease due to the multi-channel blockage of both agents and the additive effect due to the NMDA receptor antagonist feature of magnesium. A possible link was found between magnesium deficiency and migraine. Low magnesium levels have been shown in the blood, blood cells, and saliva of migraine patients[17]. The reduced intracellular magnesium concentration in the cortex of migraine patients is demonstrated using 31P-magnetic resonance spectroscopy (31P-MRS)[18]. 400-600 mg/day Mg^{+2} was observed to be effective in reducing the frequency of migraine episodes and pain duration[19, 20]. The recommended dosage in acute migraine episodes is 1-2 g, and it is recommended especially in treatment-resistant or severe migraine episodes. In a study carried out with dosage of 1 g, 87% of the patients responded with an administration for 15 minutes[11]. Although its role in the pathogenesis of migraine is still unknown, it can be tried as a rescue treatment option in acute cases.

Our aim in this study was to find a treatment option that could be given in a hospital setting providing a strong analgesic effect with fewer side effects. Therefore, we wanted to evaluate the effectiveness of the double combination at a lower dose. This combination study is a first for medication overuse

headache and its efficacy should be supported by double-blind randomized studies that also include scales such as the Comprehensive Headache-related Quality of life Questionnaire (CHQQ) with larger patient series[21].

Despite all these limitations, an 1-hour combination of lidocaine-magnesium may be considered as an alternative option for the patient to have a more quality detoxification process during the hospital stay, so that in parallel to the reduction in the use of multiple treatments (such as neuroleptics, benzodiazepine, antiemetics and opioids) and duration length of stay, the economic costs can also be reduced. In addition, the administration of lidocaine and magnesium combination will bring fewer side effects compared to their separate administration.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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