DOI: *http://dx.doi.org/10.22122/ahj.v12i4.285* *Published by Vesnu Publication*

Effect of Magnesium Sulfate Added to Tincture of Opium and Buprenorphine on Pain and Quality of Life in Women with Dysmenorrhea: A Prospective, Randomized, Double-blind, Placebo-controlled Trial

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Original Article

Abstract

Background: Adding magnesium sulfate ($MgSO_4$) to opioid receptor agonists increases the opioid analgesic effects via blocking this receptor. The current study aimed to evaluate the effectiveness of adding $MgSO_4$ to tincture of opium (TOP) and buprenorphine (BUP) on pain and quality of life (QOL).

Methods: In prospective, randomized, double-blind, placebo-controlled clinical trial, one hundred and sixty-three women with secondary dysmenorrhea caused by endometriosis were selected using a respondent-driven sampling (RDS) and assigned into six groups using block randomization. Patients received 50 mg/kg $MgSO_4$ in 100 ml saline by micro set in six monthly menstrual periods and completed the visual analogue scale (VAS) and QOL Questionnaire (QOLQ). Data were analyzed by repeated measures analysis of variance (ANOVA) and hierarchical regression.

Findings: The primary outcomes showed that pain scores in magnesium (MAG) + opium tincture (OT) [$F = 5.7(1,162)$, $P = 0.004$] and MAG+ BUP [$F = 4.5(1,162)$, $P = 0.006$] groups showed a significant decrease compared with control group. Also, QOL scores in MAG + OT [$F = 4.8(1,162)$, $P = 0.005$] and MAG + BUP [$F = 5.9(1,162)$, $P = 0.003$] showed a significant increase. However, there was no significant difference between the two groups ($P = 0.140$) and the changes did not persist until follow-up ($P = 0.810$). Secondary outcomes indicated that the low scores of the two components of QOL including physical and psychological components were predictors of pain ($P = 0.011$, Beta > 3.09).

Conclusion: Simultaneous use of MAG with opioids is associated with pain reduction and the improvement of QOL. However, this hypothesis requires careful handling in a randomized controlled trial.

Keyword: Dysmenorrhea; Endometriosis; Pain; Magnesium sulfate; Buprenorphine

Citation: Pirnia B, Masoudi R, Pirnia K, Jalali M, Eslami MR, Malekanmehr P, et al. **Effect of Magnesium Sulfate Added to Tincture of Opium and Buprenorphine on Pain and Quality of Life in Women with Dysmenorrhea: A Prospective, Randomized, Double-blind, Placebo-controlled Trial.** Addict Health 2020; 12(4): 259-68.

Received: 17.05.2020 **Accepted:** 23.07.2020

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Introduction

Dysmenorrhea is one of the most common gynecological conditions that is experienced during menstruation.[1] Dysmenorrhea is associated with abdominal cramping, back pain, nausea, vomiting, diarrhea, and headache that leads to high social and economic costs for the person.[2] Recently, a systematic review has found that the prevalence of dysmenorrhea is over 70% in Iranian girls.[3]

Dysmenorrhea consists of two primary and secondary types. Primary dysmenorrhea refers to menstruation pain without underling pathology, while secondary dysmenorrhea is associated with menstruation pain with underling pathology. Endometriosis is one of the main causes of secondary dysmenorrhea. Endometriosis is a chronic disease that affects 2 to 17 percent of women of reproductive age.[4] Endometriosis means endometrial glands and stroma outside the uterus. Symptoms of endometriosis include dyspareunia and chronic pelvic pain. Pelvic pain is often associated with a menstrual period, and may begin before the menstrual period, continue for several days after the menstrual period, and become worse over time. Gastrointestinal (GI) symptoms of endometriosis are diarrhea, constipation, rectal bleeding, and dyschezia. Increasing the amplitude and basal pressure tone of uterine contractions along with endometriosis lesions and adhesions in these patients are some of the causes of pain. In terms of pain mechanism, the prostaglandin concentration in the menstruating blood of women with endometriosis is higher than that of the normal individuals. Life with endometriosis is extremely painful and represents a struggle for coherence. Affected women need to deal with conflicting feelings and injured lives that require a double search to find the meaning.[4] It has been shown that this disease extremely affects the quality of life (QOL).[5,6] Endometriosis has a negative impact on the components of QOL such as physical functioning, social function, emotional well-being, sexual intercourse, energy and vitality, employment, and infertility in women.[4] It can be said that endometriosis has significant social and psychological effects on women's lives. Also, previous studies have shown that high score of pain is the predictor of low QOL in women with endometriosis.[7]

Pain management practices are an important concept in the field of gynecology and obstetrics. In addition to special conditions after surgery such as cesarean section and hysterectomy, caring for patients under chronic pain conditions, such as endometriosis, is very important in this field.[8] Today, the use of analgesics and opioids in the treatment of pain has been studied. One of the most effective drugs for pain is opioid receptor agonists that have been used in pain management.[9] Tincture of opium (TOP) or opium syrup, also called laudanum, is a brownish red drug and is one of the herbal drugs made with alcohol that contains about 10% opium powder, equivalent to 1% of morphine, and includes all opium alkaloids, morphine and codeine. TOP is used for opioid dependency and pain management.[10] Buprenorphine (BUP) is a mixed agonist-antagonists drug and acts on the brain to stop the symptoms of sudden drug discontinuation. The results of the studies show that BUP has been effective in treating moderate to severe pain.[9]

On the other hand, magnesium (MAG) is an intracellular ion with diverse physiological functions in humans. MAG is the fourth most commonly-used cation in the body, which plays a role in many important functions such as enzyme activity, deoxyribonucleic acid (DNA) and protein synthesis, vaso-motor tone regulation, and neuromuscular excitability.[11]

MAG is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that is effective in pain and its continuity. The pharmacological form of MAG is magnesium sulfate (MgSO4). MgSO4 has been studied in the form of NMDA antagonist in reducing acute postoperative pain and decreasing postoperative opioid use in different clinical situations such as orthopedic, gynecological surgery and preventing or reducing dysmenorrhea pain and its usefulness has been reported.[12] Studies have shown that MAG has an effect on inflammatory and neuropathic pain in animal models. The early mechanism of MAG effects on the pain seems to have been caused by blocking NMDA receptor in the spinal cord. MAG also has the potential of calcium channel blocking and modulating potassium channel.[13]

The combination of MgSO4 and opioid agonists can be considered as pharmacological innovations. Previous studies have confirmed the effectiveness of the combination of MgSO4 and morphine, bupivacaine, opioid, and Ketamine.[14,15] New evidence suggests that the combination of MgSO4 with morphine at 30 minutes before anesthesia

significantly reduces pain and morphine consumption after surgery in patients.[16,17] The results of the study by Farzanegan et al.[14] showed that co-use of MgSO4 and bupivacaine and morphine after tracheotomy was associated with reduction of pain and the need for opioid use. Kizilcik and Koner[15] showed that using MgSO4 reduced postoperative pain and opioid use in obese patients undergoing gastrectomy. Also, Forget and Cata[18] showed that the combination of MAG and Ketamine was effective in improving postoperative pain and reducing drug use. Also, the results of a meta-analysis study showed that intravenous (IV) magnesium prior to surgery reduced analgesia after cesarean.[19]

In contrast, the results of the study by Maleki et al.[20] showed that MgSO4 was not effective in reducing the pain of renal colic. Also, the results of the study by Martin et al.[21] showed that the addition of MAG to remifentanil did not significantly reduce pain scores compared to the addition of methadone to remifentanil, and the addition of MAG alone reduced the need for postoperative opioids. The results of the study by Sahmeddini et al.[22] showed that the combination of tramadol and lidocaine compared with the combination of MgSO4 and lidocaine increased the postoperative analgesia and reduced analgesic consumption.

Today, the prescription of opioids has become an epidemic of substance abuse with the goal of managing the disease. Despite the importance of the responsible use of opioids in pain management, this is not a guarantee of the safety of these interventions. The use of opioids, in addition to the risk of addiction and the development of tolerance, is associated with side effects such as constipation, dizziness, dizziness and cognitive disorders. Due to the multiplicity of side effects, it is advisable that these drugs should not be prescribed with the aim of reducing pain.

Assessing the risks and avoiding excessive dependence on drugs are issues that require clinical attention.[8] This suggests the need for effective interventions in pain management. Considering the use of opioid agents for pain relief, in our study, we used patients under maintenance treatment along with non-user women. We studied three hypotheses: Does the prescription of MgSO4 to women with opioid non-dependence with dysmenorrhea reduce pain and improve the QOL in them? Does adding MgSO4 to TOP and BUP reduce pain and improve the QOL? And finally, whether the pain scores are the predictors of QOL in these patients or not.

Methods

Sample and setting: In this study, we used a prospective, randomized, double-blind, placebo-controlled trial with a 6-month follow-up. During February 2017 to June 2018, one hundred and sixty-three (n = 163) women, including 57 women with a clinical suspicion of endometriosis referring to 7 clinics in Tehran, Iran, and 106 women with endometriosis diagnosis and under BUP maintenance treatment or TOP, were non-randomly selected from 9 addiction treatment clinics through respondent-driven sampling (RDS)[23], which is a combination of chain sampling and a mathematical model (Markov chain theory and network bias), and were invited to the research after obtaining the required criteria. One hundred and sixty-three participants were assigned to 6 groups by nature and randomly, through block randomization method. Block randomization is a commonly-used technique in clinical trial design to reduce bias and achieve balance in the allocation of participants to treatment arms, especially when the sample size is small.[24]

In this study, there were three experimental groups (MgSO4) and three control groups (normal saline as placebo). The first and second groups were the users of TOP which one group received MgSO4 (n = 26) and the second group received placebo (n = 28). The third and fourth groups were BUP users which the third group received MgSO4 (n = 27) and the fourth group received placebo (n = 25); and the fifth and sixth groups were opioid non-users. The fifth group received MgSO4 (n = 29) and the sixth group received placebo (n = 28) (Figure 1). Since the type of research was double-blind, during the intervention process, assessment, and analysis, blindness was observed.

The inclusion criteria were: age of 18-45 years, the presence of regular menstrual cycle, features of pelvic endometriosis (posterior, middle, and anterior compartments), and taking 2-4 cc of TOP and 2-4 mg BUP sublingual. Exclusion criteria were: hypersensitivity to MgSO4, 18 > body mass index (BMI) > 35 kg/m^2, previous surgical treatment, hormonal therapy in the last 6 months, use of drugs affecting neuromuscular function, history of renal disease, hepatitis, current pregnancy, hypomagnesemia (serum magnesium concentration < 1.8 mg/dl), and hypermagnesemia (serum magnesium concentration > 2.6 mg/dl).

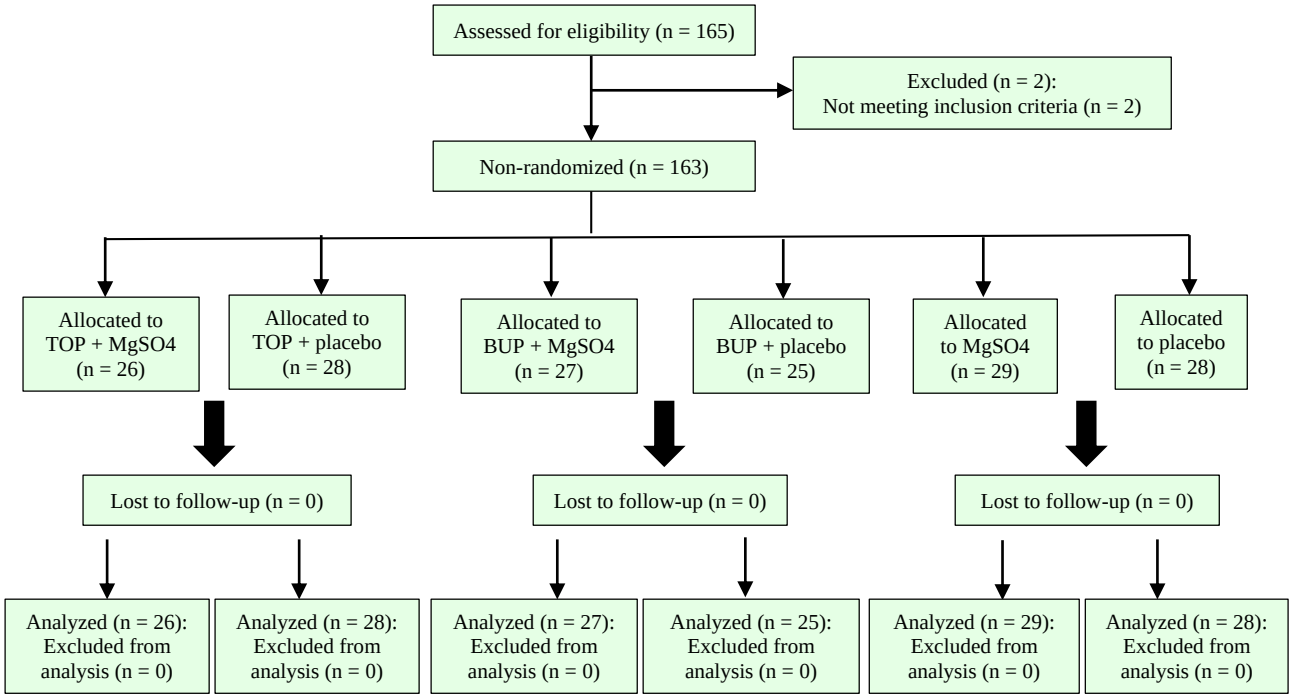

Figure 1. Flow diagram of the progress through the phases of a placebo-controlled clinical trial
MgSO4: Magnesium sulfate; TOP: Tincture of opium; BUP: Buprenorphine

Measurements: The Structured Clinical Interview for DSM-5 (SCID-5): Twenty-one days before the intervention, during the evaluation, a structured clinical interview was conducted by a clinical psychologist (PhD holder) and an addiction therapist for addiction disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The criterion for negative morphine urine test (Abon Rapid Test) was assessed for the BUP group. Also, in the TOP group, the opium test (Abon Rapid Test) was performed. Also, all psychiatric diagnoses were approved by a psychiatrist in order to reach a diagnostic agreement.

QOL Questionnaire (QOLQ): The QOL was evaluated by the QOL instrument [The World Health Organization Quality of Life (WHOQOL-BREF)]. This is a 26-item short questionnaire containing two items for general QOL and health status and 24 items categorized in four dimensions (physical, psychological, social, and environmental). The range of item scores is from 1 to 5, which the highest score indicates the better QOL. The scores for each dimension range between 4-20.[7] A critical value of 60 is considered as the optimal cut-off point for assessing perceived QOL and satisfaction with health. In study of Yousefy et al.[25] for the total sample, the internal consistency of the domains was satisfactory to good, yielding Cronbach's alpha ranging from 0.78 for psychological health to 0.82 for social relationships. The Cronbach's alpha for the entire sample, the clinical, and the non-clinical was 0.82, 0.82, and 0.84, respectively.

Visual analogue scale (VAS): The VAS is the most widely used pain measurement tool in the world.[26] This scale measures pain on a continuum in the range of 0-100. The study results of Boonstra et al.[27] showed that VAS scores $\leqslant$ 3.4 corresponded to mild interference with functioning, whereas 3.5 to 6.4 implied moderate interference, and $\geqslant$ 6.5 implied severe interference. In the study of Pirnia et al.,[26] test-retest reliability and sensitivity to change were optimally reported.

Weight and body fat measurements: Regarding the role of BMI in the severity of dysmenorrhea, all participants were screened in terms of height, weight, and fat by Seca Supra Plus 720 column scale (Seca, Hamburg, Germany) and the data were analyzed by bioelectrical impedance analysis (BIA). BMI was considered based on body height and body weight and in a range of 18-35 kg/m^2.

Intervention: Patients in the experimental group received 50 mg/kg MgSO4 50% IV (diluted in 100 ml normal saline). Control group received

20 cc of normal saline (infused with the same volume as the experimental group). The peak effect of BUP and TOP is 120 minutes after consumption. The effect of MgSO4 also initiates immediately after IV injection and its effect lasts 30 minutes. Regarding the peak of the effect time of maintenances, prescription of MgSO4 was performed at one hour and forty-five minutes to two hours and fifteen minutes after the morning use of maintenance. Regarding the regularity of the cycle of menstruation, 12 hours prior to the beginning of the first day of the period, the reminder SMS was automatically sent to the participant, and at the scheduled time, the study team including a physician, a registered nurse (RN), and an emergency medical technician (EMT) was referred to the patient's home and the injection of MgSO4 (or placebo) was performed by micro set for ten minutes.

The absorption of MgSO4 in IV injection is rapid and the duration of action is about 30 minutes.[28] Therefore, immediately after receiving MgSO4, VAS was completed by the participant. The QOLQ was completed by the participant on the last day of the period. This process was carried out for six monthly periods. Side effects of injection resulted from MgSO4 were assessed in the form of two groups: 1) pain and burning at injection site and 2) feelings of drowsiness, heat, and transpiration. In the event of an increase in heart rate (HR) and arterial blood pressure (BP), more than 20% of the systolic BP (SBP), injection of IV fentanyl (1.2 µg/kg) was carried out to restore HR and arterial pressure to normal levels, and data of that participant was excluded from the analysis process.

The data were analyzed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA). The data were analyzed using Shapiro–Wilk test for assessing the normality of the data. The distribution of demographic and clinical variables was normal in both groups and at all times. Repeated measures analysis of variances (ANOVA) was used to test the difference between the six groups on pain scores and QOL in multiple time intervals. We used hierarchical linear regression to determine whether pain was associated with low levels of QOL in people with different age and BMI. In the stage one, the variables of age and BMI were introduced into the equation. In the second step, pain scores were introduced into the equation. Eventually, in the third stage, the scores of QOL were introduced into the equation. Since dysmenorrhea is influenced by age, weight, and fat, these variables were controlled in all analyses. Demographic characteristics were evaluated in two groups by chi-square test.

Ethical consideration: This study was approved and clinically recorded by Shahid Beheshti University of Medical Sciences, Tehran. All stages of the study were carried out after obtaining informed consent from the participants and based on the Declaration of Helsinki.[29] This trial was registered at the www.clinicaltrials.in.th (TCTR20190329001). The study adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Results

Participant characteristics: Among 211 enrolled patients in our trial, 48 patients were excluded from the study. One hundred and sixty-three people were entered into the research process with an average age of 29.0 ± 2.8 years. Hemodynamic factors including HR, respiratory rate (RR), and BP had no significant changes after intervention and had similar levels in the groups. Characteristics for participants in each study group are presented in table 1.

QOL and pain scores: Data related to primary outcomes were compared between MAG + TOP, MAG + BUP, MAG alone, normal saline + TOP, normal saline + BUP, and normal saline alone in table 2.

As it can be seen in table 2, the results of repeated ANOVA showed reduction of pain variable and significant increase of QOL variable in two groups of opium tincture (OT) + MAG and BUP + MAG in comparison to MAG alone, OT alone, BUP, and normal saline ($P < 0.01$).

Table 1. Demographic characteristics of the study groups

Variable	TOP		BUP		Non user		Pairwise comparisons
	+ MAG	+ normal saline	+ MAG	+ normal saline	+ MAG	+ normal saline	
Age (year)	29.12 ± 3.79	32.21 ± 4.19	33.51 ± 3.51	28.74 ± 3.79	28.59 ± 4.73	31.39 ± 3.62	NS
BMI (kg/m^2)	24.73 ± 2.52	26.11 ± 4.09	23.75 ± 2.84	25.72 ± 3.22	25.89 ± 4.07	23.04 ± 3.11	NS

Data are presented as mean ± standard deviation (SD)

BMI: Body mass index; MAG: Magnesium; TOP: Tincture of opium; BUP: Buprenorphine; NS: Not significant

Table 2. Repeated measures analysis of variance (ANOVA) results for pain and quality of life (QOL) scores in six groups after 6 months

Variable	Components	TOP		BUP		Non user	
		+ MAG	+ Normal saline	+ MAG	+ Normal saline	+ MAG	+ Normal saline
VAS		60 (6.2)*	65 (6.8)	61 (5.9)*	64 (5.7)	68 (7.3)	69 (7.2)
QOL	Physical	14 (2.1)*	11 (1.2)	13 (1.8)*	11 (1.4)	9 (1.1)	8 (1.3)
	Psychological	15 (2.8)*	11 (1.4)	14 (2.2)*	12 (1.5)	10 (1.3)	10 (1.2)
	Social	13 (1.9)*	10 (1.2)	14 (2.1)*	11 (1.2)	11 (1.2)	10 (1.4)
	Environmental	12 (1.6)*	10 (1.1)	12 (1.7)*	10 (1.3)	9 (1.1)	8 (1.0)

*P < 0.01

VAS: Visual analogue scale; QOL: Quality of life; MAG: Magnesium; TOP: Tincture of opium; BUP: Buprenorphine

At baseline, experimental and control subjects did not differ significantly in state pain and QOL scores. Repeated measures ANOVA showed a significant time-group interaction in MAG + OT [F = 5.7(1,162), P = 0.004] and MAG + BUP [F = 4.5(1,162), P = 0.006] for state pain and MAG + OT [F = 4.8(1,162), P = 0.005] and MAG + BUP [F = 5.9(1,162), P = 0.003] for QOL (Figure 2). However, there was no significant difference between the two groups (P = 0.14).

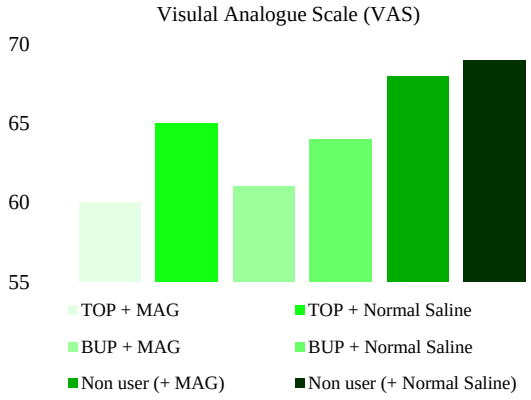

Figure 2. Visual analogue scale (VAS) scores in six groups

We used a hierarchical linear regression to examine the relationship between the total score of QOLQ and pain. The two components of physical and psychological were the predictors of pain (P < 0.011, Beta > 3.09). No significant relationship was observed between age and pain and QOL (P > 0.05). Also, in three participants, feelings of drowsiness and in two participants, the symptoms of transpiration were observed; each of the five participants was non-user of opioids.

Discussion

This study was conducted aiming to evaluate the effectiveness of adding MAG to TOP and BUP on pain and QOL in women with dysmenorrhea under maintenance treatment who were non-dependent. The results showed reduction of pain and significant increase of QOL variable into two groups of MAG + OT and MAG + BUP in comparison with the other four groups (MAG alone, normal saline, normal saline + OT, and normal saline + BUP). However, there was no significant difference between the two groups. Also, the low scores of the two physical and psychological components were the predictors of pain. However, no significant relationship was found between age with pain and QOL.

Although this study is the first study to investigate the addition of MAG in the field of addiction, many studies suggest an increase in the analgesic effects of MgSO4 and opioid agonists. In line with the results of the present study, the results of the study by Naderi et al.[16] and Jarahzadeh et al.[17] showed that the composition of MgSO4 with morphine at 30 minutes before anesthesia significantly reduced pain and morphine consumption after surgery in patients. Also, in line with our results, the results of the study by Farzanegan et al.[14] showed the analgesic effect of adding MgSO4 to morphine in reducing postoperative pain. Also, the results of the study by Farzanegan et al. showed that co-use of MgSO4 and bupivacaine and morphine after tracheotomy was associated with decreased pain and the need for opioid use. Also, the results of the study by Kizilcik and Koner[15] showed that prescription of MgSO4 was accompanied by reduction of pain and opioid use after operation under gastrectomy. In this regard, the results of the study by Forget and Cata[18] showed that the combination of MAG and Ketamine was effective in improving postoperative pain and reducing drug use. Also, the results of a meta-analysis study showed that IV MAG prior to surgery reduced analgesia after cesarean.[19] In contrast with our results, the results of the study by Martin et al.[21] showed that the addition of MAG to

remifentanil did not significantly reduce pain scores compared to the addition of methadone to remifentanil, and the addition of MAG alone reduced the need for postoperative opioids. Also, the results of the study by Maleki et al.[20] showed that MgSO4 was not effective in reducing the pain of renal colic. Contrary to our results, the results of the study by Baaklini et al.[30] showed that the addition of MAG to morphine in patients with cancer did not have a significant effect on pain and QOL.

A part of the results of this study showed that low scores of QOL including two physical and psychological components were predictors of pain. In line with our results, the results of the study by Shim et al.[31] showed that pain perception in patients with rheumatism was associated with a decrease in the quality of physical and psychological life. In this regard, da Silva et al.[32] in a study showed that pain was correlated with QOL in all its dimensions.

A part of our results showed that there was no significant relationship between age and pain and QOL. Contrary to our results, da Silva et al.[32] showed that being young was a protective factor against pain in patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).

Research evidence suggests that there is a clear link between MAG deficiency and the occurrence of symptoms in a number of conditions, including premenstrual syndrome (PMS), menstrual migraine, and dysmenorrhea. MAG seems to be involved in blocking the receptor in the spinal column, blocking the calcium channel, and modulating the potassium channel with analgesic effects. Adding MAG may reduce the dose of the opioid and, as a result, reduce its side effects.

The short duration of the follow-up and the small size of the sample are among the limitations of our study. The use of self-reporting tool and non-probability sampling (RDS) were as important limitations of this study. In RDS method, generalizability to the underlying population is hard to establish. It is suggested that in the future studies, biomarker be used to evaluate the studied variables.

Conclusion

The results of this study showed that the addition of MgSO4 to TOP and BUP reduced pain and improved QOL in women with dysmenorrhea. It is suggested that in future studies, the effectiveness of the addition of edible MAG in the form of supplement to opioids be investigated.

Conflict of Interests

The authors have no conflict of interest.

Acknowledgements

The authors would like to thank the Preventative Gynecology Research Center, Shahid Beheshti University of Medical Sciences for their support, cooperation, and assistance throughout the period of study.

Authors' Contribution

Study concept and design: BP, LA, FP; analysis and interpretation of data: KP, RM, MJ; drafting of the manuscript: BP, MRE, KP, RM; critical revision of the manuscript for important intellectual content: KP; statistical analysis: BP, MJ, MRE; administrative, technical, and material support: BP, PM, LA, FP; study supervision: BP.

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DOI: *http://dx.doi.org/10.22122/ahj.v12i4.285* *Published by Vesnu Publication*

اثر منیزیم سولفات افزوده شده به تنتور اپیوم و بوپرنورفین بر درد و کیفیت زندگی زنان دارای دیسمنوره: یک کارآزمایی آینده‌نگر، تصادفی، دوسوکور، کنترل شده با دارونما

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مقاله پژوهشی

چکیده

مقدمه: افزودن منیزیم سولفات به آگونیست‌های گیرنده‌های اپیوئید، اثرات بی‌دردی آن را از طریق بلوکه‌سازی این گیرنده افزایش می‌دهد. پژوهش حاضر با هدف ارزیابی اثربخشی افزودن منیزیم سولفات به تنتور اپیوم و بوپرنورفین بر درد و کیفیت زندگی انجام شد.

روش‌ها: در این کارآزمایی آینده‌نگر، تصادفی، دوسوکور و کنترل شده با دارونما، ۱۶۳ زن مبتلا به دیسمنوره ثانویه ناشی از آندومتریوز، با استفاده از روش نمونه‌گیری پاسخ محور انتخاب شدند و از طریق تصادفی‌سازی بلوکی به شش گروه تخصیص یافتند. بیماران ۵۰ میلی‌گرم بر کیلوگرم منیزیم در ۱۰۰ میلی‌لیتر نرمال سالین را به کمک میکروست در شش دوره قاعدگی ماهانه دریافت نمودند و Visual analogue scale (VAS) و پرسش‌نامه کیفیت زندگی را تکمیل نمودند. داده‌ها با استفاده از آزمون Repeated measures ANOVA و رگرسیون سلسله مراتبی مورد تجزیه و تحلیل قرار گرفت.

یافته‌ها: نمرات درد در گروه‌های منیزیم + تنتور اپیوم [(۱۶۲، ۱) F = ۵/۷، P = ۰/۰۰۴] و منیزیم + بوپرنورفین [(۱۶۲، ۱) F = ۴/۵، P = ۰/۰۰۶] کاهش معنی‌داری را در مقایسه با گروه شاهد نشان داد. همچنین، نمرات کیفیت زندگی در گروه منیزیم + تنتور اپیوم [(۱۶۲، ۱) F = ۴/۸، P = ۰/۰۰۵] و منیزیم + بوپرنورفین [(۱۶۲، ۱) F = ۵/۹، P = ۰/۰۰۳] افزایش معنی‌داری داشت. هرچند، تفاوت معنی‌داری بین دو گروه مشاهده نشد (P = ۰/۱۴۰) و تغییرات تا مرحله پیگیری پایدار نماند (P = ۰/۸۱۰). نتایج ثانویه نشان داد که نمرات پایین در دو مؤلفه فیزیکی و روان‌شناختی کیفیت زندگی، درد را پیش‌بینی نمود (P = ۰/۰۱۱، Beta > ۳/۰۹).

نتیجه‌گیری: استفاده هم‌زمان از منیزیم و اپیوئیدها با کاهش درد و بهبود کیفیت زندگی همراه بود. هرچند این فرضیه به بررسی دقیق در قالب یک کارآزمایی بالینی تصادفی نیاز دارد.

واژگان کلیدی: دیسمنوره؛ آندومتریوز؛ درد؛ منیزیم سولفات؛ بوپرنورفین

ارجاع: پیرنیا بیژن، مسعودی راحله، پیرنیا کامبیز، جلالی مینا، اسلامی محمدرضا، ملکان مهر پرستو، پیرنیا فریبرز، آجری لادن. **اثر منیزیم سولفات افزوده شده به تنتور اپیوم و بوپرنورفین بر درد و کیفیت زندگی زنان دارای دیسمنوره: یک کارآزمایی آینده‌نگر، تصادفی، دوسوکور، کنترل شده با دارونما.** مجله اعتیاد و سلامت ۱۳۹۹؛ ۱۲ (۴): ۶۸-۲۵۹.

تاریخ دریافت: ۱۳۹۹/۲/۲۸ **تاریخ پذیرش:** ۱۳۹۹/۵/۲

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