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The Effect of Magnesium Lozenge on Pain, Oedema and Trismus after Impacted Third Molar Surgery: A Prospective Randomized, Double-Blinded, Placebo-Controlled Study

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Abstract

Background: The postoperative sequelae after third molar surgery include pain, swelling and trismus, Magnesium has antinociceptive effects that can prevent central sensitization caused by peripheral nociceptive stimulation by blocking the N-methyl-D-aspartate-type glutamate receptors. Studies have investigated Magnesium for postoperative pain relief. This study was aimed to evaluate the efficacy of oral Magnesium lozenge given 30 min before surgery on reducing postoperative sequelae.

Method: We recruited 70 patients, randomly assigned to two groups: Magnesium and Control group, groups received 100mg Magnesium lozenge, placebo lozenge 30 min before surgery respectively and every 6h till 72h after surgery. Third molar extraction was performed under local anesthesia. After extraction, pain, swelling, and mouth opening in both groups observed till 72h.

Statistical Analysis: Preoperative and postoperative measurement of visual analog scale scores for pain, edema, interincisal opening, was analyzed using Student t test or ANOVA, Chi-square or Mann-Whit¬ney U test was performed for non-parametric samples. $P < 0.05$ was considered as statistically significant

Results: The overall incidence of Pain in the Magnesium group was 18% compared to 43% in the Control group ($P = .003$) Incidence of Pain, swelling, and mouth opening at different time intervals 6h, 24h, 48h and 72h were significantly ($P > 0.05$) better in Magnesium group.

Conclusion: Oral Magnesium lozenge administered 30 minutes preoperatively can significantly reduce postoperative sequelaeafter third molar extraction.

Keywords: Postoperative sequelae; Third molar; Magnesium.

Introduction

Third molar extractions are one of the most common and basic outpatient interventions in oral and maxillofacial surgery.[1] Depending on the location, depth, tooth angulation and bone density, the complexity of surgical extraction may vary, and is generally associated with postoperative sequelae.[2] Recently some strategies have been developed for minimizing postoperative discomfort after third molar surgery, including the use of pharmacological therapy and alternative medicine[3] and complementary protocols like minimally-invasive tooth extraction have been suggested for the postsurgical therapy of third molar surgery.[4]

However, patients still suffer some pain, swelling, and limitation in mouth mobility and other symptoms after surgery.Reducing dental malaise and postoperative complications is a critical issue for oral and maxillofacial surgery doctors.[5]

Magnesium has antinociceptive effects that are primarily based on the inhibition of calcium entry into the cell, and blocks the N-methyl-D-aspartate-type (NMDA) glutamate receptors.[6,7] Therefore; magnesium can prevent central sensitization caused by peripheral nociceptive stimulation. Although previous studies regarding pain have generally focused on the role of spinally located NMDA receptors, NMDA receptors are also known to exist peripherally[8] and it is possible that inflammation stimulates peripheral NMDA receptors. Oral route of magnesium, including lozenge form, had been investigated for its efficacy in acute rescue treatments in postoperative pain.[9]

At present, the clinical evidence regarding the effect of Magnesium is sparse. In lightof these findings, this study was conducted to compare the efficacy of oral Magnesium lozenge given 30 min before surgery on reducing pain during 3 days after surgical extraction of mandibular third molars.

Materials and Methods

This prospective randomized controlled trial was conducted during May 2019 and April 2020. It was reviewed and approved by the Institutional Ethics Committee; we recruited 70 patients after obtaining written informed consent, before the beginning of this study with mandibular-impacted third molar. Inclusion criteria: age between 18 and 30 years, American Society of Anesthesiology (ASA) score of 1 (i.e., no systemic diseases or medical conditions), no active pathology associated with the third molars, no acute pericoronitis, and no periodontal disease. Exclusion criteria: contraindications of surgery; long-term administra-tion of medication, recent administration of steroids, oral and systemic antibiotics, or repeated pericoronitis of the tooth; caries of moderate degree of the wisdom and adjacent teeth; periapical periodontitis, pulpitis, or periodontitis, anti-platelet or anticoagulant therapy, pregnancy or lactating, recent local infection within 15 days prior to surgery.

Sample size calculated by analyzing previous studies, presuming the incidence of postoperative pain to be 65%. Using power analysis, as per the sample-size calculation 31 patients per group would be required to detect a minimum of 50% reduction in the incidence of postoperative pain, with alpha= 0.05 and $\beta = 0.20$ for two-tailed statistical analysis. Therefore, we included thirty five patients in each group. We divided patients equally and randomly into Magnesium group and Control group, using a computer randomization generator, each with 35 patients. Perioperative treatment for patients in the two groups was conducted using the double-blind method. Before surgery all patients routinely examined and dental X-ray film was obtained before surgery. The extent of swelling, limitation of mouth opening index, and data related to procedure were measured before surgery.

All patients in the group received Lozenge 30 min before surgery, followed by every 6th hour for 72hrs.

1. Group M (Magnesium group) (n=35) - oral Magnesium lozenge (100mg).
2. Group C (Control group) (n=35) - oral lozenge as placebo.

Magnesium lozenge-610 mg magnesium in form of citrate salt, containingmagnesium ion 100 mg content per dose, citric acid, sucrose, cellulose powder, calcium canoate, xanthan gum, sodium cyclamate, aromatics, and colorant, Placebo lozenge- containing sucrose, sodium free, and calcium with xylitol, glucerin and which is indistinguishable in appearance and taste from the one containing Magnesium lozenge. Lozenge will be provided by the one staff nurse and subsequent assessment of the patient by different staff nurse. Patients and operating surgeon will not be aware of the study drug.

All surgical procedures were performed by one oral and maxillofacial surgeon; aseptic scrubbing and draping were done. Under strict aseptic precautions, 2 ml of 2% lignocaine with 1:2,00,000 adrenaline was used for an inferior alveolar nerve block, following the hospital's protocol. Additionally, infiltration anesthesia was administered in the buccal fold and distal of the incision in the mandibular ramus region.

A standard Ward's incision or a modified Ward's incision was given regularly for all the cases. In cases where visible intraoral crown or part of crown of the tooth, a standard ward's incision was placed. In cases if tooth was completely covered by mucosa, modified ward's incision was placed. To eliminate bias, we used only modified ward's incision for both control and study side. To expose the tooth and surrounding bone a full-thickness mucoperiosteal flap was raised. we used a round bur and a straight fissure bur no 701, for guttering buccal bone. The arc of rotation was determined and analyzed

usingpreoperative radiographs. If interference to removal was found on analysis, sectioning was done using a no 703 straight fissure bur. After extraction, granulation tissue, follicular remnants and bony spicules were removed from the socket and closure done in both groups with 3-0 silk sutures. Patients were given both verbal and written postoperative instructions after surgery. Patients in both groups were provided with an ice pack for postoperative cooling, and were prescribed 3-day course of amoxicillin + clavulanate 1000 mg-twice daily, all patients were given comprehensive instructions on the importance of maintenance of oral hygiene and jaw physiotherapy postoperatively.

Detection of indexes and evaluation. The visual analog score (VAS) was adopted to evaluate the pain degree of patients. The score range was 0-10 (0 for no pain and 10 for intolerable severe pain) severe: ≥7 points for intolerable pain, patients took a combination of ibuprofen 400 mg + Paracetamol 325 mg 1 tablet, The patient marked the appropriate response on the scale at 24 h, 48 h and 72h after surgery.

The measurements were obtained using a flexible ruler in the pre and post-operative periods of 6, 24, 48 and 72h. The sum of the pre-operative measurements was considered the standard of normality for each side. The measurements from the post-operative period was verified, the difference between before and after the surgical procedure measurements was observed, determining the level of oedema.

Trismus was evaluated by measuring the maximum buccal opening. Using a digital caliper transcribed in millimeters, we measured the maximum inter-incisional vertical distance (distance between the surfaces of the upper and lower right central incisors) after maximum opening without aid, pre-operatively and 6h, 24h, 48h and 72 h post-operatively. The measurements were compared to the baseline. Thus, the relative mean (Delta) was calculatedfor each patient between the final and initial measurements.

Statistical calculations were conducted using SPSS (Statistical Package for the Social Sciences) Version 24.0 (IBM Corporation, Chicago, USA). The parametric variables were present¬ed as mean ± SD and analyzed by Student t test or ANOVA and Pearson correlation test as appropriate, Chi-square or Mann-Whitney U test and Spearman correlation coefficients was performed for non-parametric samples. $P<0.05$ was considered as statistically significant.

Results

A total of 70 patients were included in the study and randomly assigned to one of the groups. Thirty five patients received Magnesium and 35 received placebo lozenge. There were no significant differences between two groups of patients with respect to age, sex, and BMI (Table 1).

Table 1: Demographic Characteristics of Patients in Two Groups.

Variables	Magnesium (mean±SD)	Control (mean±SD)	P Value
Age (Year)	29.2+8.6	27.4+10.8	0.44
Male (%)	57.1	51.4	0.63
Weight (Kg)	74.4+12.6	75.2+12.8	0.79
BMI (kg/m2)	22.4+3.2	23.1+4.2	0.43

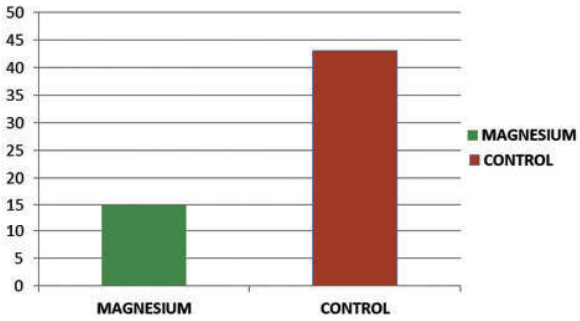

Fig. 1: Over all incidence of pain.

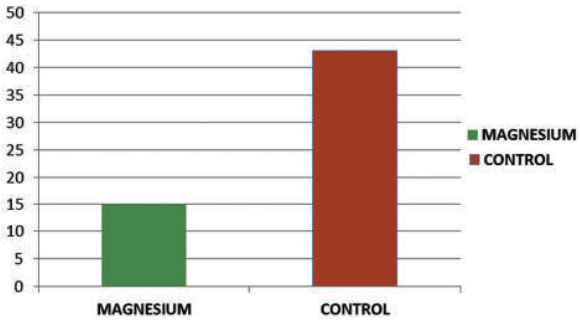

Fig. 2: Incidence of pain at different time intervals.

The overall incidence of Pain in the Magnesium group was 15% shown in green (Fig. 1) compared to 43% in the Control group shown in red ($P = .010$) using generalized estimating equation with binomial probability distribution, logit link function, and autoregressive (AR) working correlation matrix resultant in odds ratio (95% confidence interval), 6.568 (6.711 to 46.758). Error bars represent 95% confidence interval.

Incidence of Pain in the Magnesium group is shown in green (Figure-2) and the Control group in red. At time 6h, incidence of Pain in Magnesium

group was 0% compared to 24% of the Control group (adjusted P = .002); since the incidence of Pain at 6 hour in Magnesium group was 0, the Hessian matrix was singular and some convergence criteria not satisfied, an accurate 95% confidence interval (CI)or odds ratio (OR) could not be reported; at time interval 24 hours, incidence of Pain was 8% in the Magnesium group compared to 34% in the Control group (adjusted P = .008) with OR 7.029 (95% CI, 6.877- 43.401); at time interval 48 hours, incidence of Pain was 9% in the Magnesium group compared to 29% in the Control group (adjusted P = .034) with OR 4.483 (95% CI, 1.390- 37.490); and at time interval 72 hours, the incidence of Pain was 11% in the Magnesium group compared to 24% in the Control group (adjusted P = .155) with OR 2.019 (95% CI, 0.204- 30.570).

Table 2: Pain by VAS Scale.

Group	Postoperative day 1	Postoperative day 2	Postoperative day 3
Magnesium	5.42+0.74	4.13+1.02	2.18+0.64
Control	6.06+1.23	4.73+1.25	2.76+1.17
t-value	2.637	2.2	2.573
p-value	0.01	0.031	0.012

Table 3: Swelling degree after surgery.

Group	Postoperative day 1	Postoperative day 2	Postoperative day 3
Magnesium	2.18+0.26	1.34+0.16	0.26+0.16
Control	2.85+0.43	1.98+0.27	1.01+0.37
t-value	7.888	12.064	11.007
p-value	<0.0001	<0.0001	<0.0001

Table 4: Limitation of mouth opening.

Group	Postoperative day 1	Postoperative day 2	Postoperative day 3
Magnesium	2.18+0.26	1.34+0.16	0.26+0.16
Control	2.85+0.43	1.98+0.27	1.01+0.37
t-value	7.888	12.064	11.007
p-value	<0.0001	<0.0001	<0.0001

Using generalized estimating equation with AR working correlation matrix and binomial probability distribution, P < .05 was considered statistically significant.

According to the VAS scores of pain (Table II) after surgery, the Magnesium group exhibited significantly lower scores at all measured time points compared to the control group, indicating more efficient pain reduction.

In terms of swelling degree (Table III) after surgery, even though swelling decreased in both groups from day 1 to day 3 after surgery. However, the Magnesium group exhibited significantly lower swelling compared to control group at each time point measured, indicating more efficient swelling management. The limitation of mouth opening degree (Table IV) decreased in both groups from day 1 to day 3 after surgery. However, the Magnesium group exhibited significantly lower scores than the Control group at each time point measured, indicating more efficient functional recovery after third molar surgery.

Discussion

The rate of complications in general after extraction of third molars can reach up to 20%. Therefore, a key priority for dentists in these procedures is to effective prevention of these complications.[10] These symptoms include pain, dry socket, face swelling, limited mouth opening, and other, typically last for seven days causing serious impact on the daily life of patients.[11] The pathology of pain results from damaged tissues, which irritates the nerves. Edema and swelling of the face as part of the normal reactive edema after destruction of tissue during surgery. Moderate swelling is a protective reaction to trauma; however, excessive swelling has damaging consequences and even leads to infection.[12] The limited mouth opening is that cutting soft tissue during surgery irritates the temporal tendon and the muscle in nasal alar, causing a reflex spasm explains the mechanism of trismus.[13] Treatment of complications after tooth extraction include cold-hot compress, oral administration of non-steroidal anti-inflammatory drugs. These treatments need to extend for a period after surgery to shorten the durations of pain, swelling, and limited mouth opening. The inflammatory response is the most basic reaction to injuries and is a necessary stage for injury repair after third molar extraction.[14]

The results of the present study showed overall incidence of 15% of Pain in group Magnesium, while in Control group overall incidence of Pain was seen in 43% of the study subjects, Moreover, in our study there was a significant difference in Pain at 6h, 24h, 48h & 72 hour between Magnesium and Control (p<0.05). In the Magnesium group, The implication of magnesium in pain reduction lies in its ability to serve as a noncompetitive NMDA receptor antagonist by preventing extracellular calcium movement into the cell and by attenuating central sensitization. Specifically, the blockade of glutamate and aspartate at the NMDA receptor by magnesium is the central mechanism.[15] In addition to the effects of magnesium on NMDA receptors,

it blocks calcium channels, resulting in potentially clinically beneficial peripheral vasodilation, bronchodilation, and uterine relaxation via its effects on smooth muscle, and demonstrated post-operative analgesia.[15] This likely explains the significant difference in the incidence of Pain between the groups. The present study showed that oral Magnesium lozenge administered 30 min before surgery reduced the incidence of Pain, Swelling, and Trismus till 72h after surgery. Although the use of Magnesium did not decrease the incidence of Pain in patients, it decreased the intensity of Pain. Our study is similar to the study by Jerkovic D et al, conducted study on 80 participants using different oral forms of magnesium citrate. Posted for surgical removal of two lower molars, the results show a statistically significant lower pain level at all tested times (24h, 48h, and 72h postoperatively) for participants who used magnesium preparations in lozenges and concluded that orally administered magnesium (either lozenges or tablets) before and after a lower third molar surgical removal significantly reduces pain intensity and the degree of trismus in the postoperative period.[16]

Sudama Prasad D et al,conducted a prospective, observational study in 120 Patients undergoing elective surgery of approximately 2 h or more duration under GA requiring tracheal intubation. Patients in the study group were nebulized with 3 ml of 225 mg isotonic nebulized magnesium sulphate for 15 min in the holding area. There was a significant difference in Post Operative Sore Throat (Post) at rest between group at 4h,10h and 24h. Concluded that the use of magnesium sulphate in the form of nebulization as a pre-medication agent significantly reduces the incidence of Post compared to normal saline and it was found to be safe, simple and effective in preventing the occurrence of postoperative sore throat.[17]

A review article by Narinder P Singh et al, showed that incidence of post at 24 hours was significantly lower in patients taking magnesium, with no significant adverse events with the use of topical magnesium. Concluded that prophylactic use of topical magnesium before the induction of general anaesthesia is an effective measure to decrease the incidence of post.[18]

Borazan H et al, studied seventy patients undergoing orthopedic surgery received magnesium lozenges to be dissolved by sucking 30 min preoperatively and observed thatthe The severity of post was significantly lower in the magnesium group at 0 and 2h, concluded that the administration of magnesium lozenge 30 min preoperatively is effective to reduce both incidence and severity of post in the immediate postoperative period.[19]

In these above-mentioned studies, it was suggested that the reduction in the incidence and severity of Pain, Swelling & Trismus was related with anti-inflammatory effects of the administered drugs. Similar to these previous studies, our study found that the Magnesium lozenge has reduced incidence and severity. Our study suggests that patients who received a single dose Magnesiumpreoperatively showed decreased symptoms with increased time (in the first 6 hours) and showed reduced incidence. Nevertheless, comparisons of the effectiveness of these treatments were performed in only a low number of small studies. Studies examining the comparative effectiveness of Magnesiumversus other pharmacological drugs in preventing postoperative sequelae are still warranted.

Conclusion

In conclusion oral Magnesium lozenge administered 30 minutes preoperatively can reduce complications after third molar extraction, including pain, swelling, and limited mouth opening. Besides, Magnesium can promote the recovery effect, improve the quality of life after surgery, and its administration is convenient, easy, economic, and has non-invasive characteristics that deserve wider clinical attention and application.

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Conflicts of interest: There are no conflicts of interest.

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