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The effects of intra-articular $MgSO_4$ in osteochondral lesions: An experimental study

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ABSTRACT

Objectives: The aim of the study was to assess the efficacy of intra-articular administration of $MgSO_4$ in an osteochondral lesion model created experimentally in rabbits. *Methods:* A total of 22 New Zealand rabbits were used in the study for the creation of a standard osteochondral lesion in the right femur medial condyles. Twice a week for periods of 6 and 8 weeks, $MgSO_4$ (0.1ml) at a dose of 500µg was injected intra-articularly to the magnesium group and 0.1ml saline solution to the control group. At 2 weeks after the final injection, all the animals were euthanised. An osteotomy was performed to include the region where the osteochondral defect was formed, and each sample was placed in 10% formalin solution. Morphological evaluation and scoring was performed. The samples were stained with hematoxylin-eosin and safranin-O, then histopathological evaluation and scoring was performed. *Results:* The histopathological scores of the Mg-6-week group were determined to be significantly higher than those of the control-6-week and control-8-week groups (p=0.025, p=0.012). The macroscopic scores of the Mg-6-week group were determined to be significantly higher than those of the control-6-week group (p=0.003). In the histological examination, the osteochondral defect area of the Mg groups showed intense healing from hyalin cartilage whereas in the control group, healing was seen to be weighted towards fibrous cartilage. *Conclusion:* The intra-articular administration of $MgSO_4$ in the osteochondral lesion model created experimentally in rabbits was determined to have made a positive contribution to histopathopathological and morphological healing.

Keywords: $MgSO_4$, Cartilage, Osteochondral lesion, Experimental Study, Intra-articular

1. INTRODUCTION

Joint cartilage injury and degeneration is frequently seen in synovial joints. The treatment of joint cartilage lesions is difficult because this tissue cannot regenerate easily and of good quality. Chondral lesions are frequently seen in arthroscopy applied following acute joint trauma (Felson et al., 2000; Simon & Jackson, 2018; Hjelle et al., 2002). Many different medical and surgical treatments have been applied and attempted for the treatment of osteochondral lesions which have developed (Chubinskaya et al., 2015). There

is 25g of magnesium in the human body and a large proportion of this is found in bone, cartilage, muscle, and other soft tissues, and a very small amount has been determined in the blood. Magnesium, which is one of the critical cations in the body, plays a significant role in a variety ofphysiological and enzymatic activities (Evrensel, 2017; Kuang et al., 2021). Magnesium sulphate is a well-known pharmacological agent, which is used in many clinical conditions. MgSO4 is used in conditions such as tachyarrhythmia, myocardial and neurological ischaemia, asthma, spasm, pre-eclampsia, and post-anaesthesia shivering (Delhumeau et al., 1995).

Previous studies have reported that the administration of intra-articular MgSO4 following arthroscopic surgery controls pain and could be considered as an alternative to local anaesthetics (Zeng et al., 2016; Altay et al., 2010; Zou et al., 2016; Orak et al., 2015). Magnesium prevents synovitis and reduces pain by suppressing inflammatory processes in the joint. It increases cartilage matrix synthesis and decreases cartilage degeneration, thereby providing an anti-osteoarthritic effect. It also prevents chondral autophage and apoptosis. Magnesium demonstrates chondroprotective activity, especially when applied intra-articularly (Yue et al., 2019).

Although the chondroprotective and analgesic effect of MgSO4 is known in experimental osteoarthritis models, the early and late-term efficacy in acutely developing osteochondral defects remains a subject of interest.

2. MATERIAL AND METHODS

Approval for the study was granted by the Local Ethics Committee. The study started in May 2021 and was completed in January 2022. The study sample was formed of a total of 22 New Zealand rabbits, each weighing mean 3200 g (3000-3450 g), and older than 9 months. The rabbits were randomly assigned to four groups as magnesium- 6 weeks, magnesium -8 weeks, control-6 weeks, and control-8 weeks. Each of the control groups included 5 rabbits and each of the magnesium groups, 6 rabbits. From one week before the operation until the day of sacrifice, all the rabbits were under the observation of a veterinary surgeon. All the animals were housed in single cages at 22° and a 12-hour light-dark cycle, with unlimited access to tap water and standard rodent feed. A standard cartilage defect model was created in the right femur medial condyle of each rabbit (Chu et al., 2010; Kilkenny et al., 2010; Cook et al., 2014). Antibiotic prophylaxis was administered during or after the operation. No wound site infection developed in any rabbit during the follow-up period.

Injections were administered twice a week by the same person using an insulin injector as 500μg MgSO4 0.1 ml to the magnesium group and 0.1 ml saline to the control group (Shimaya et al., 2010; Kikuchi et al., 1998). The injections were performed for 6 weeks to the Mg-6-week and the control-6-week groups and for 8 weeks to the Mg-8-week and the control-8-week groups. At 2 weeks after the final injections, the animals were sacrificed. Then the distal femur region was osteotomised to include the area where the chondral defect was created. The osteotomised distal femur was placed in 10% formalin solution and prepared for the histopathological and morphological evaluations.

Surgical Tecnique

The necessary preparations were made then the rabbits were admitted to the operating room. Each rabbit was weighed and the appropriate anaesthetic dose was calculated. Intramuscular administration of Ketamine 6mg/kg to the right hip region was performed as anaesthesia. When a sufficient depth of anaesthesia was reached, the right knee region of the rabbit was shaved, then on the opereating table the right knee region was stained with 10% povidone iodine and sterile draped. A parapatellar 2cm incision was made in the medial right knee and the distal skin was passed to reach the subcutaneous fascia. The joint capsule was opened from the medial patella, then by everting the patella laterally, the knee was brought into flexion. The femur medial condyle was exposed. An osteochondral lesion, 3.2mm in diameter and 3mm in depth, was created in the femur medial condyle appropriate to the standards defined in literature (Chu et al., 2010; Kilkenny et al., 2010; Cook et al., 2014; Ahern et al., 2009).

Following bleeding control, the joint capsule was sutured with 3-0 polyglactin sutures. The wound site was closed with a skin stapler and wiped wth povidone, then the operation was terminated. The animals were transferred from the operating table to the follow-up unit (Figure 1).

Macroscopical evaluation

The surrounding soft tissues of the knee joints were dissected carefully without any texture to the knee joint. Morphology of trauma-induced joint face was macroscopically scored according to the scoring system of International Cartilage Repair Society (ICRS) evaluation scores (Van den Borne et al., 2007). This system has a maximum total macroscopical score of 24 and higher scores indicate normal or minimum cartilage damage.

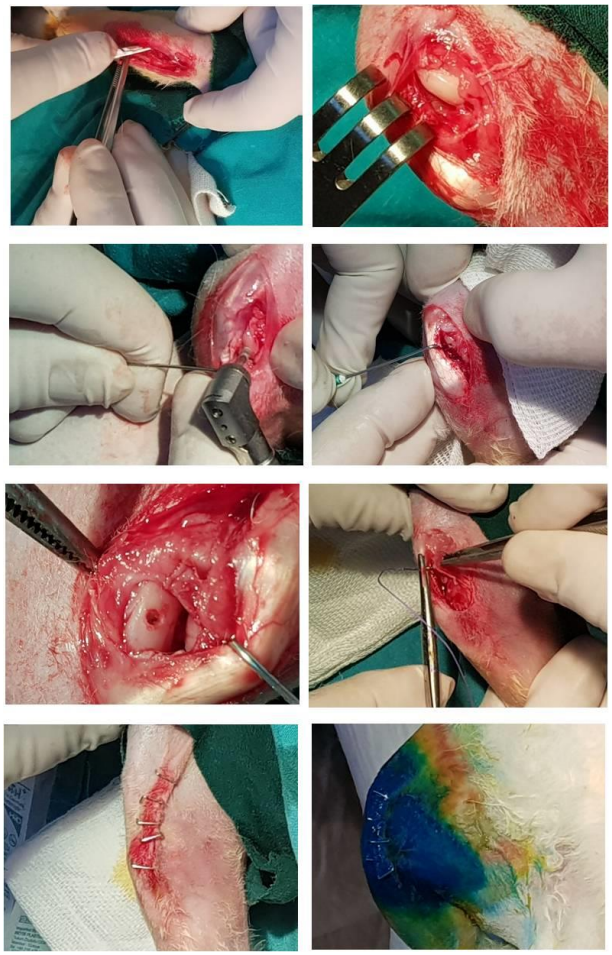

Figure 1 Establishing an osteochondral lesion model in the rabbit medial femoral condyle

Histopathological evaluation

After macroscopic evaluation and sampling, the tissue specimen was fixed in 10% formaldehyde solution for 24-hours and kept in formic acid for 24-hours for decalcification. The specimen was then sampled as a 3-4 mm thick intact tissue covering the damaged area and surrounding healthy tissue. Tissues were embedded in paraffin blocks; 5-10 sections were taken from each sample with a microtome each of 4 to 5 micron which was stained with hematoxylin-eosin. Additionally, one section of each sample was stained with safranin O dye by keeping deparaffinized slides in xylene for 10 minutes. Then after, placed in 100% alcohol for 5 min, in 95% alcohol for 1 min, and in 70% alcohol for 1 min. Slides were stained for 10 minutes with Weigert's Iron hematoxylin solution and washed for 10 minutes with running water. Slides were kept in safranin O solution for 5 min., rinsed with distilled water and kept in Fast Green solution for 10 min. Slides were placed in acetic acid solution for 10-15 sec, in 95% alcohol for 1 min, and in two 100% alcohol stations for 5 min. Finally, slides were cleaned with xylene before evaluation. Histopathological evaluation of the cartilage tissue was performed according to scoring system of O'Driscoll et al., (1988). Under the Nikone Eclipse light microscope by the same blinded pathologist. The maximum total histopathological score was 24 and higher scores indicate normal or minimum cartilage damage.

Statistical methods

Statistical analyses were performed with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA, Licence: Hitit University) software. Descriptive statistics were presented with median (min-max) and mean±standard deviation (SD) in accordance with non-parametric tests. The Shapiro-Wilk test was used to test the normal distribution of the data. Kruskal-Wallis test was used to compare histopathological and macroscopic scores between the rat groups, since parametric test assumptions were not met. Following a significant Kruskal-Wallis test, Dunn-Bonferroni post-hoc tests were used for pairwise comparisons to identify groups that differed. $p<0.05$ value was considered statistically significant.

3. RESULTS

The histopathological scores showed a statistically significant difference between the rabbit groups (p=0.005) (Table 1). According to the post-hoc test results, the histopathological scores of the Mg-6-week group were determined to be significantly higher than those of the control-6-week and control-8-week groups (p=0.025, p=0.012, respectively). No statistically significant difference was determined between the histopathological scores of the other groups (p>0.05) (Table 1). The boxplot showing distribution of the histopathological scores of the groups is shown in Figure 2.

Table 1 Comparison of histopathological scores between rat groups

Groups	n	Median (min-max)	Mean±SD	*P* values	Post hoc *P* values
$MgSO_4$ (6 weeks)	6	19 (16-23)	19±2.82	0.005*	1-2: 1.000
$MgSO_4$ (8 weeks)	6	16 (12-18)	15.33±2.42		1-3:0.025*
Control (6 weeks)	5	11 (6-16)	11±5		1-4:0.012*
Control (8 weeks)	5	12 (10-12)	11.4±0.89		2-3: 0.597
					2-4: 0.362
					3-4: 1.000

* Kruskal Wallis test with Dunn-Bonferroni post hoc test

SD: Standard deviation

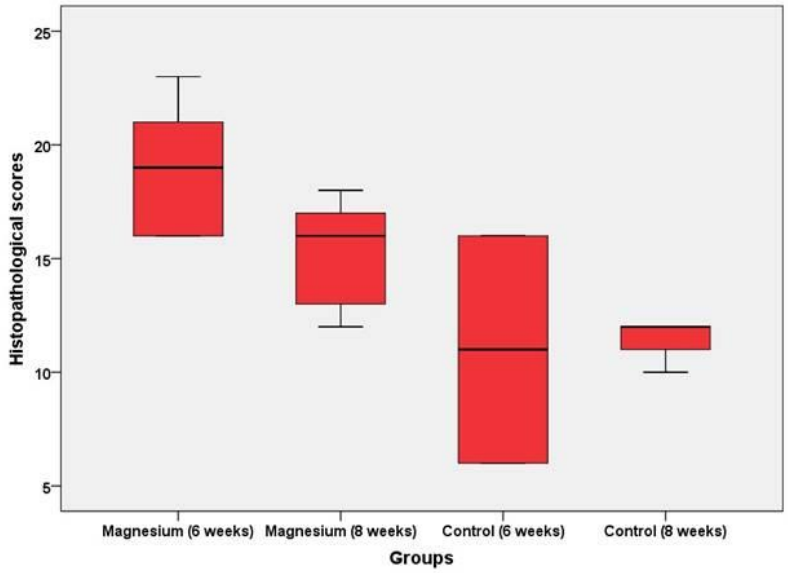

Figure 2 Boxplot for the comparison of the distribution of histopathological scores among rat groups

Table 2 Comparison of macroscopic scores between rat groups

Groups	n	Median (min-max)	Mean±SD	*P* values	Post hoc *P* values
$MgSO_4$ (6 weeks)	6	13.5 (11-18)	13.83±2.63	0.005*	1-2: 1.000
$MgSO_4$ (8 weeks)	6	11.5 (9-13)	11.33±1.63		1-3:0.003*
Control (6 weeks)	5	7 (6-10)	7.6±1.81		1-4: 0.311
Control (8 weeks)	5	11 (7-12)	10.2±1.92		2-3: 0.133
					2-4: 1.000
					3-4: 0.844

* Kruskal Wallis test with Dunn-Bonferroni post hoc test

SD: Standard deviation

The macroscopic scores were determined to be statistically significantly different between the groups (p=0.005) (Table 2). According to the post-hoc results, the macroscopic scores of the Mg-6-week group were determined to be significantly higher than

those of the control-6-week group (p=0.003). No statistically significant difference was determined between the macroscopic scores of the other groups (p>0.05) (Table 2). The boxplot showing distribution of the macroscopic scores of the groups is shown in Figure 3. Histopathological images of MgSO4 and control groups are shown in Figure 4.A and 4.B.

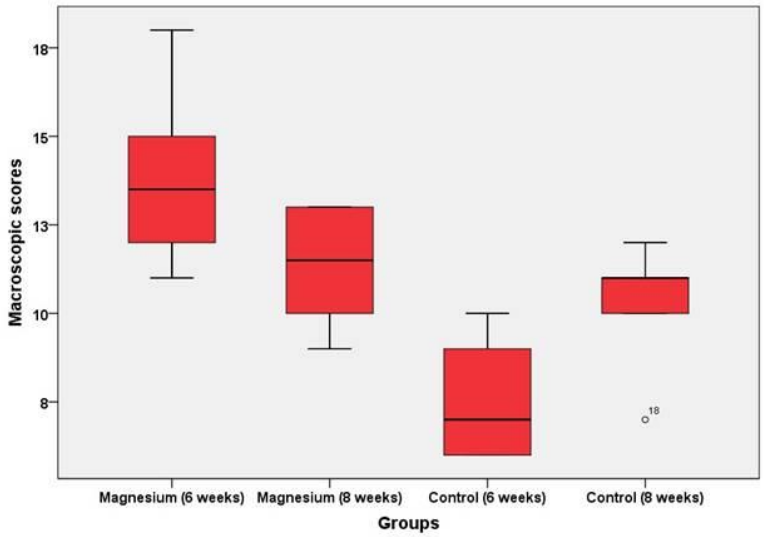

Figure 3 Boxplot for the comparison of the distribution of macroscopic scores among rat groups

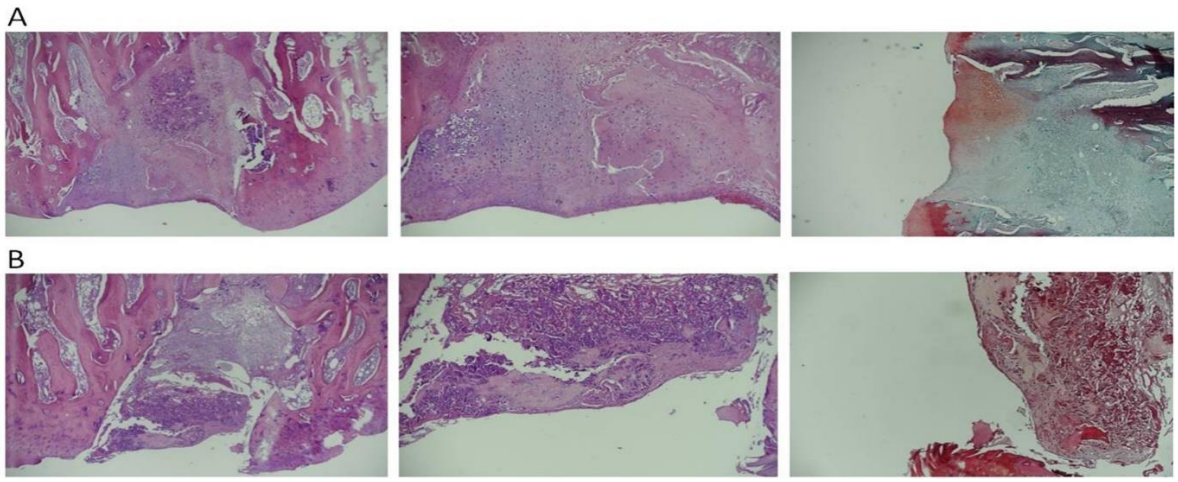

Figure 4 A. In the sections of the MgSO4 (6 weeks) group, the neoformed cartilage tissue, which is slightly sunken on the surface, is continuous with the surrounding cartilage at both ends, mostly composed of hyaline cartilage, and shows significant chondrocyte clustering, and a slightly decreased safranin-o staining in this cartilage compared to the surrounding cartilage (H-Ex40, 100 and safranın O40) **B.** Defect area that is predominantly composed of fibrous tissue, depressed from the surface, and does not show neoformed cartilage formation in the sections of the control (8 weeks) groups. (H-Ex40, 100 and safranin O40)

4. DISCUSSION

There are 3 basic components of joint cartilage, which are the matrix scaffold, cells, and signal molecules. Creation of joint cartilage compatible with these three components is an obstacle to be overcome for ultimate success (Hunziker et al., 2015). In the repair of osteochondral lesions that have developed in the joint, Mg is an important signal molecule. Chondrocytes are cells found in healthy cartilage (Szychlinska et al., 2017), and Mg plays an important role in the inflammatory process that develops in the joint cartilage (Kuang et al., 2021). In ex-vivo analyses and in-vivo studies by Shimaya et al., (2010) it has been reported that magnesium increased the adhesion of synovial mesenchymal stem cells mediated by integrins, to the cartilage defect area and thus increased the formation of cartilage. The osteochondral defect was created in the trochlear region.

Feyerabend et al., (2006) showed that chondrocytes induced with the addition of MgSO4 responded to high extra-cellular magnesium concentrations with an increase in gene and protein expression levels and an associated increase in chondrocyte

proliferation and re-differentiation. It has been reported that a high Mg2+ concentration can prevent ECM calcification in a dose-dependent manner, and by preventing autophage, a chondrogenesis protective effect is shown (Yue et al., 2019). When the current study results are examined in this framework, magnesium could be an agent with high potential for the healing of osteochondral lesions. Hyalin cartilage is a tissue which does not contain innervation and blood vessels. Treatment modalities applied after chondral lesions may not completely provide an appropriate balance between chondrocyte proliferation and differentiation. In several ongoing experimental and clinical studies, it has been seen to be extremely difficult to recreate hyalin cartilage. By combining different approaches including advanced structure scaffolds, chondrocytes which have been effectively differentiated, 3D printed structures and approaches which affect the appropriate fatty and proinflammatory environment, regeneration of the joint cartilage can be improved to a great degree (Medvedeva et al., 2018).

Repair tissue is formed at 6-8 weeks after osteochondral injury. Therefore, the minimum time until investigation of osteochondral tissue repair should vary between 4 and 6 weeks (Buckwalter, 2002). The healing ability of articular cartilage is limited (Figure 4A). Washing, debridement, abrasion, perforation of the subchondral bone, or microfracture of the joint triggers the formation of fibrous cartilage instead of hyaline (Korkusuz et al., 2010). Although the regeneration of osteochondral defects is difficult, the histopathological appearance of the MgSO4 group in the current study showed that more intense healing from hyalin cartilage had been achieved (Figure 4B). In osteochondral defects that develop acutely, $MgSO_4$ could form cartilage regeneration with dense hyalin cartilage, and this was thought to be an important finding.

In the current study, the macroscopic and histopathological healing scores of the $MgSO_4$ group were significantly higher than those of the control group in a 6-week period. By suppressing the inflammatory processes in the joint, magnesium prevents synovitis and reduces pain. It increases cartilage matrix synthesis and decreases cartilage degeneration, thereby providing an anti-osteoarthritic effect. It also prevents chondral autophagy and apoptosis. Magnesium demonstrates chondroprotective activity, especially when applied intra-articularly (Yue et al., 2019). In the immunohistochemical examination in experimental osteoarthritis models, Lee et al., (2009) found that MgSO4 treatment suppressed synovitis, prevented chondrocyte apoptosis, and diminished the development of OA. In an experimental OA model created in rats, Yao et al., (2019) reported that intra-articular injections of Mg2+ significantly improved cartilage degeneration and synovitis. This was explained by Mg promoting cartilage matrix synthesis and suppressing synovial inflammation. However, this does not fully explain the underlying mechanisms and specific effects of Mg2+ supplementation for OA treatment. The histomorphometric characteristics in both cartilage and synovium and therapeutic effects on cellular pathogenesis of Mg2+ were not evaluated in that study.

In a different post-traumatic model OA model, an intra-artcular injection of magnesium sulphate reduced intra-articular inflammation and was found to support cartilage regeneration in rabbits (Chen & Zhou, 2018). The anti-osteoarthritic effects and effect mechanisms were evaluated in an experimental OA model in the current study. In literature, there are extremly few studies showing the efficacy of Mg in acutely formed osteochondral lesions (Kuang et al., 2021). Osteoarthritis is chronic process which progresses with joint cartilage degeneration, and positive effects have been obtained with Mg. However, moreresearch is needed to investigate the potential of MgSO4 as a therapeutic agent and see the positive effects in acutely developing osteochondral lesions. The intra-articular administration of Mg after arthroscopic knee surgery reduces the need of patients for postoperative analgesia and alleviates pain, suggesting that it may be an alternative to local anaesthetics (Delhumeau et al., 1995; Bondok & El-Hady, 2006; Noha et al., 2009). There is also a need to investigate the clinical utility of MgSO4 in the treatment of OCD, which is frequently seen in arthroscopic surgery. It has been reported that both dietary and magnesium supplements and intra-articular MgSO4 injection may show cartilage protective effects because of the broad changes in the IncRNA and mRNA profile of chondrocytes (Lei et al., 2017).

In a clinical study of early stage osteoarthritis by Condello et al., (2018) a biomimetic scaffold was applied with a 3-layer structure formed from magnesium-enriched hydroxyapatite and type I horse collagen. High patient satisfaction was reported from the treatment and good, stable clinical results were obtained with a low complication rate. There was stated to be a need for further studies with larger cohorts to confirm those findings. In a study conducted on sheep and rabbits that evaluated the regeneration potential of magnesium-enriched hydroxyapatite (MgHA), collagen, and chitosan-based scaffold, it was concluded that more studies are needed to determine the best formulation for osteochondral treatment (Roffi et al., 2019). Mg should be included in the content of therapeutic composite used in osteochondral defects, and there is a need for further studies on this subject.

5. CONCLUSION

Mg can be used more effectively in osteochondral defects due to its antiosteoarthritic, anti-inflammatory, chondroprotective and chondrogenesis-enhancing effects. Mg may be the key molecule in hyaline cartilage development and therefore more research is

needed.

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Ethics approval and consent to participate
The animal studies were performed in the institute and experimental protocol was duly approved by Institutional Animal Ethical Committee (Reg No. 235/Ankara).

Authors' contributions
TA, MÇ, conceptualization, methodology, data collection, formal data analysis.
TA, MÇ, Dİ writing original draft preparation, writing review and editing, supervision, validation, and editing: All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Conflicts of interest
The authors declare that there are no conflicts of interests.

Data and materials availability
All data associated with this study are present in the paper.

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