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ORIGINAL INVESTIGATION

The effect of low dose intra-articular S(+) ketamine on osteoarthritis in rats: an experimental study

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KEYWORDS
Osteoarthritis;
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Abstract
Background: This study aimed to investigate the analgesic impact of S(+)-ketamine on pain behavior and synovial inflammation in an osteoarthritis (OA) model.
Methods: Animals were grouped as follows: OA-Saline (n = 24) and OA-Ketamine (n = 24), OA induced via intra-articular sodium monoiodoacetate (MIA); a Non-OA group (n = 24) served as the control. On the 7th day post OA induction, animals received either saline or S(+)-ketamine (0.5 mg.kg^{-1}). Behavioral and histopathological assessments were conducted up to day 28.
Results: S(+)-ketamine reduced allodynia from day 7 to 28 and hyperalgesia from day 10 to 28. It notably alleviated weight distribution deficits from day 10 until the end of the study. Significant walking improvement was observed on day 14 in S(+)-ketamine-treated rats. Starting on day 14, OA groups showed grip force decline, which was countered by S(+)-ketamine on day 21. However, S(+)-ketamine did not diminish synovial inflammation.
Conclusion: Low Intra-articular (IA) doses of S(+)-ketamine reduced MIA-induced OA pain but did not reverse synovial histopathological changes.
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Introduction

The mechanisms underlying the origin of joint pain in Osteoarthritis (OA) remain poorly understood. Articular cartilage and the meniscus are structures devoid of nerves and, therefore, cannot directly serve as sources of painful sensations. However, alterations in these structures and even in the synovial fluid could indirectly contribute to the pathophysiology of pain in OA. Fragments of cartilage containing nociceptor sensitization in these areas are likely to contribute to the initiation and persistence of pain.[1] Furthermore, distinct elements such as collagen, proteoglycans, crystals, proteolytic enzymes, or cytokines released into the synovial fluid could potentially trigger a synovial inflammatory response associated with pain. Afferent nerve fibers are present in various parts of the joint, including the joint capsule, synovium, periosteum, subchondral bone, ligaments, and tendons.[2]

Evidence from pharmacological, electrophysiological, and behavioral research indicates that glutamate receptors play a pivotal role in pain pathways. Modulation of these receptors has been implicated in various types of pain, including central and peripheral neuropathic pain as well as joint inflammatory pain. Elevated levels of glutamate have been detected in the synovial fluid of OA patients.[3,4] Additionally, glutamate's involvement as a modifier of OA has been observed, leading to increased receptor expression in cells such as osteoblasts, osteoclasts, and chondrocytes, revealing a significant role in bone and cartilage remodeling.[3]

The principal excitatory effect of glutamate within the nervous system occurs via N-Methyl-D-Aspartate receptors (NMDA), which have been identified as key contributors to central sensitization and the chronicity of pain. Animal studies have demonstrated the presence of NMDA receptors (NMDAr) in both myelinated and non-myelinated axons within somatic peripheral tissues.[4]

In a study that examined the role of glutamate signaling in chondrocytes, it was noted that these cells might express a distinctive NMDA receptor (NMDAr) with unique attributes. This receptor could potentially be involved in the inflammatory process linked to cartilage degradation, thus emerging as a promising pharmacological target in the context of OA.[5]

Effective pain management has become a therapeutic challenge in the context of osteoarthritis (OA), leading to investigations into various intra-articular (IA) drug interventions aimed at enhancing analgesia.[6] Among these interventions, racemic ketamine has been tested in various experimental OA models, indicating its potential not only in alleviating joint pain but also in mitigating inflammatory mediators and reversing histopathological changes.[7,8] The drug's primary mechanism of action, NMDAr antagonism, is widely recognized. However, its broader impacts on chronic pain management are equally significant, including the modulation of voltage-gated Na+ and K+ channels, antagonism of serotonin, norepinephrine, and dopamine reuptake, and suppression of pro-inflammatory cytokines.[9,10] Notably, S (+)-ketamine exhibits an analgesic potency four times greater than that of R(-)-ketamine due to its higher affinity for NMDAr, allowing for the use of smaller doses with minimized adverse effects.[11]

The primary objective of this study was to evaluate the analgesic effect of a low dose of S(+)-ketamine on pain behavior and the extent of synovial membrane inflammation in an experimental rat model of osteoarthritis (OA).

Methods

For the experimental phase, male Wistar strain Rattus norvegicus rats weighing approximately 230—280 g were used. The animals were acclimated and housed under controlled conditions of humidity (45—65%) and temperature (23±2 °C), with a 12-hour light/dark cycle and unrestricted access to food and water. A week before the experimental protocol began, the animals underwent daily adaptation to devices and behavioral tests.

The experiments were conducted in accordance with the guidelines of the Brazilian College of Animal Experimentation and were approved by the Research Ethics Committee of the Universidade Federal do Maranhão under protocol number 23115 012030/2009-05.

Model of osteoarthritis induced by sodium monoiodoacetate

The animals were anesthetized with sodium thiopental (40 mg.kg^{-1} intraperitoneally), followed by trichotomy of the right hind paw. Local antisepsis was performed using a 10% iodine polyvinylpyrrolidone solution. Osteoarthritis (OA) was induced in the right knee by a single intra-articular injection of 2 mg of sodium monoiodoacetate (MIA) dissolved in a maximum of 50 μL of solution. The MIA solution was administered through the patellar ligament into the intra-articular space of the right knee using a 26G needle. The left knee received an equivalent volume of saline as a contralateral control specific to the animal.[12,13]

Experimental design

In this study, 72 Wistar rats were divided into three groups. The OA-Saline Group (n = 24) and the OA-Ketamine Group (n = 24) were subjected to MIA-induced osteoarthritis. The Non-OA Group (n = 24) did not undergo osteoarthritis induction. Behavioral assessments were conducted prior to osteoarthritis induction and on the fifth day following MIA induction. On the 7th day after osteoarthritis induction, the groups received an intra-articular injection (IA) of S (+)-ketamine (0.5 mg.kg^{-1}) or 0.9% saline, with a maximum volume of 50 μL. Behavioral assessments were conducted six hours after the injection of the study solution and subsequently on days 10, 14, 18, 21, 24, and 28 after osteoarthritis induction. On days 7, 14, 21, and 28, six animals from each group were anesthetized and euthanized to harvest the synovial membrane for histopathological analysis (Fig. 1).

The main outcome was pain reduction in the ketamine group, as indicated by behavioral assessment. The secondary outcome was the effect of ketamine treatment on synovial inflammation.

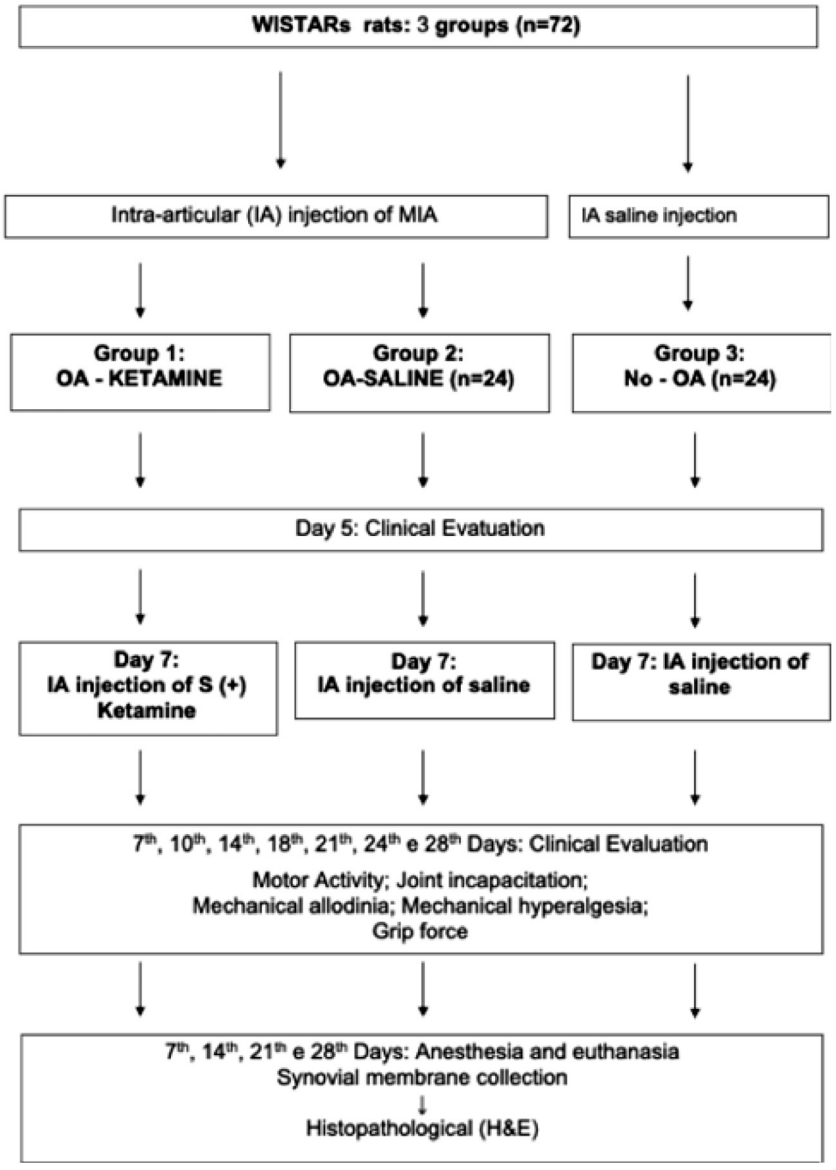

Figure 1 Study flowchart.

Behavioral assessment

Motor activity assessment/RotaRod test

The RotaRod (Model IITC Life Science, California, USA) comprises a rotating bar with adjustable speed, measured in revolutions per minute (rpm), featuring a 2.5 cm diameter and 60 cm length. Positioned 40 cm above small platforms, the rotating bar automatically stops the digital timer when animals fall off. The bar is divided into five 20 cm sections, where individual animals are placed during testing.[14]

Animals were positioned on the RotaRod, set at a speed of 16 rpm, for a duration of 300 seconds. Assessment of the affected limb's utilization was conducted through forced walking, and the utilization of the paw was rated using a numerical scale spanning from 5 to 1, where: 5 – corresponds to the limb's normal use; 4 – slight lameness; 3 – severe lameness; 2 – sporadic non-use of the affected paw; and 1 – complete non-use of the affected paw.[14]

Disability test/Hind leg weight distribution (weight bearing test)

Changes in weight distribution between the right (OA+) and left (OA) hind legs were indicative of discomfort due to MIA-induced OA. A disability test apparatus (Model IITC Life Science, California, USA) with a sensor linked to a small platform was used to gauge the animal's weight distribution on its hind legs.[14,15]

The animals were positioned within an angled glass chamber, ensuring that each hind leg rested on distinct platforms. The weight exerted on each hind leg (measured in grams) was assessed over a span of five seconds. The ultimate measurement of weight distribution was determined by calculating the average of three measurements.[14,15]

Mechanical allodynia assessment (Von Frey test)

Mechanical allodynia was evaluated using a digital algesimeter (Model Insight, São Paulo, Brazil) equipped with a

pressure transducer connected to a digital force counter measured in grams (g). The device is calibrated to record a maximum force of 150 g, maintaining precision within 0.1 g for forces up to 80 g. The contact between the pressure transducer and the animals' paws was established using a disposable polypropylene tip with a diameter of 0.5 mm, specially designed for this purpose.[14,16]

The animals were acclimated for 15 minutes before the experiment in an acrylic box (12 × 20 × 17 cm) with a floor made of a 5 mm^2 mesh network composed of non-malleable wire that was 1 mm thick. Mirrors were positioned 25 cm below the experimental boxes to enhance visibility of the animals' plantar region. The test involved applying increasing pressure to the central area of the rat's paw until the animal exhibited a "flinch" response to the stimulated paw. The stimuli were repeated up to six times on both the ipsilateral and contralateral paws until the animal demonstrated three similar responses with a clear "flinch" after paw removal.[14,16]

The Paw Withdrawal Threshold (PWT) was determined as the percentage of force required to induce active suspension in the affected ipsilateral paw.[14,16]

Mechanical hyperalgesia (Randall Selitto test)

Mechanical hyperalgesia was evaluated by assessing the paw withdrawal threshold in response to a mechanical stimulus delivered through a pressure algesimeter (Model IITC Life Science, California, United States), following the methodology previously outlined by Randall and Selitto.[17] A wedge-shaped apparatus (with an area of 1.75 mm^2) was placed on the dorsal surface of the hind limbs, applying incremental linear pressure until the animal exhibited a response characterized by paw withdrawal. Three measurements were taken on both the ipsilateral and contralateral paws. A predefined cutoff threshold of 250 g was implemented to prevent potential tissue damage.[1,13,18]

The Paw Withdrawal Threshold (PWT) was measured in grams and defined as the force percentage required to induce removal of the affected ipsilateral paw.[1,13,18]

Grip force test

The assessment of hind leg grip force was conducted by recording the maximum force applied during gripping using a stress measurement system (IITC Life Science model, California, USA). During the test, each rat was gently restrained to allow its hind legs to grasp a wire mesh (10 × 12 cm^2) connected to a strain gauge. The rats were positioned in a manner ensuring that their front legs did not touch the strain gauge.

The evaluator then applied a rostro-caudal movement until the hind leg of the animal lost contact with the mesh. Three measurements were taken, and the results were averaged. Each rat underwent the test twice, with a 2- to 3-minute interval, to obtain the grip force values in their raw form (CFmax).[19,20]

Histopathological analysis

After administering anesthesia with sodium thiopental (40 $mg.kg^{-1}$) and euthanizing the animals, the synovial membranes were extracted and fixed in 10% buffered formaldehyde. Subsequently, they were immersed in a 5% formic acid solution for 72 hours. The samples underwent dehydration through a series of ethanol solutions and were embedded in paraffin, followed by creating 4 μm thick sections, which were later stained with hematoxylin-eosin. Inflammation was identified by the expansion of the synovial membrane due to fluid edema of a protein and fibrin nature, along with the infiltration of macrophages, neutrophils, plasmocytes, and lymphocytes.

A grading system was employed to evaluate the extent of synovial inflammation, with the following grades: Grade 0 indicating no inflammation; Grade 1 for minimal inflammation; Grade 2 for mild inflammation; Grade 3 for moderate inflammation; and Grade 4 for marked inflammation.[15,21] All samples were assessed blindly by the same pathologist.

Statistical analysis

The results of behavioral tests were analyzed using One-way ANOVA, followed by the Tukey test. Intra-group comparisons at different time points during the experiment were conducted with the Friedman test. The Kruskal-Walli's test was applied to compare the results related to synovial inflammation, followed by the Dunn post-hoc test for multiple comparisons. A significance level of $p < 0.05$ was used to determine statistical significance, and data analysis was performed using GraphPad Instat® software (GraphPad Software, San Diego, CA).

Results

Effect of S(+)-ketamine on forced ambulation

Five days after MIA injection, the rats exhibited a decrease in RotaRod test scores, with a significant reduction in the OA-Ketamine and OA-Saline groups. Following the administration of S (+)-ketamine (0.5 $mg.kg^{-1}$), the animals demonstrated an improvement in forced walking, which showed statistical significance on the 14th day post OA induction. By the 18th day, all groups exhibited similar performance on the RotaRod test (Fig. 2).

Effect of S(+)-ketamine on weight distribution on hind legs

Following the MIA injection, the animals began exhibiting sings of joint discomfort, resulting in a predominant weight distribution on the healthy paw. S(+)-ketamine significantly alleviated the impairment in weight distribution from the 10th day of OA induction until the conclusion of the experiment, which spanned approximately three weeks. Starting from the 14th day, no notable distinction was observed between the OA-Ketamine group and the Non-OA group (Fig. 2).

Effect of S(+)-ketamine on mechanical alodinia

The animals developed mechanical allodynia after OA induction, as demonstrated by the Von Frey test. Treatment with S(+)-ketamine (0.5 $mg.kg^{-1}$-IA) reduced the intensity of allodynia from the 7th to the 28th day, when the difference between the OA-Ketamine and OA-Saline groups remained

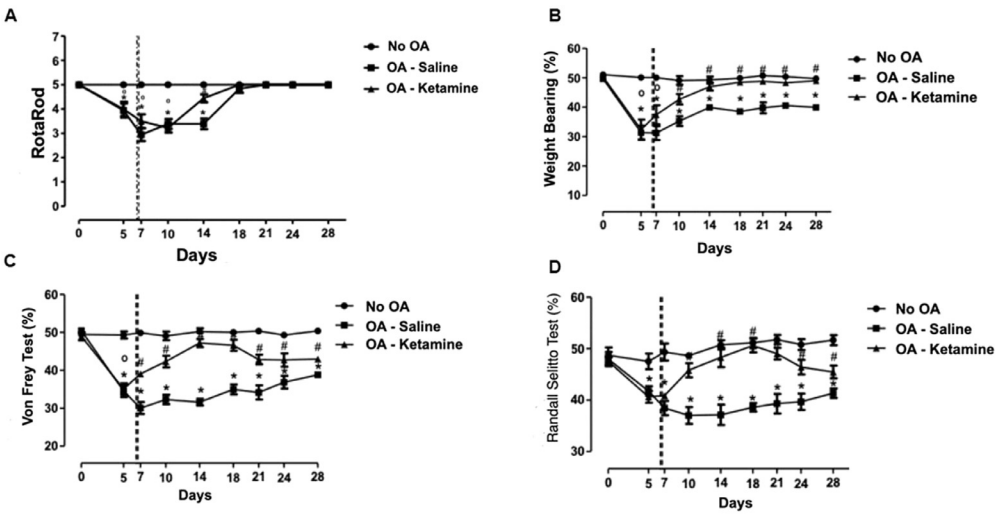

Figure 2 Results concerning the impact of S(+)ketamine in the experimental tests conducted within this study. (A) Forced Ambulation. (B) Hind Leg Weight Distribution. (C) Paw Withdrawal (Mechanical Allodynia). (D) Paw Withdrawal (Mechanical Hyperalgesia). Vertical symbols and lines denote the mean and standard error of means. The vertical dashed line signifies the beginning of treatment. * Significant difference between the OA-Saline group and the Non-OA group. ° Significant difference between the OA-Ketamine group and the Non-OA group. # Significant difference between the OA-Ketamine group and the OA-Saline group. Statistical significance: $p < 0.05$.

significant. On the 14th and 18th days, there was no significant difference between the OA Ketamine and Non-OA groups (Fig. 2).

Effect of S(+)-ketamine on mechanical hyperalgesia

The animals also exhibited the development of mechanical hyperalgesia after MIA injection, as indicated by the decrease in the paw withdrawal threshold during the Randall Selitto test. Treatment with S(+)-ketamine mitigated hyperalgesia from the 10th to the 28th day, in comparison to the OA-Saline group. From the 14th to the 24th day, the S (+)-ketamine group demonstrated complete reversal of hyperalgesia, producing results akin to those of the Non-OA group (Fig. 2).

Effect of S(+)-ketamine on grip force

Following MIA injection, the grip force of the animals decreased after the 14th day of induction. Treatment with S (+)-ketamine led to an increase in grip force from the 21st day to the 28th day, exhibiting a statistically significant difference when compared to the Saline group. On the 21st and 28th days, there were no significant differences between the OA-Ketamine and Non-OA groups (Fig. 3).

Effect of S(+)-ketamine on synovial membrane inflammation

The injection of MIA induced histopathological changes in the synovial membrane. Throughout the experiment, a significant difference was observed between the Saline-treated group and the group without osteoarthritis; however, this difference was not observed between the OA-Ketamine group and the group treated with OA-saline. Additionally, there were no significant differences within each group at different time points during the experiment. It is important to note that the group treated with ketamine did not exhibit any histopathological damage (Table 1). The maximum degree of inflammation was characterized by the expansion of the synovial membrane and the infiltration of inflammatory cells such as macrophages, neutrophils, and lymphocytes, as depicted in Figure 4H. Figure 4D displays an intact and healthy section of the synovial membrane, while Figure 4L represents a graded degree of inflammation with a score of 3 (Fig. 4).

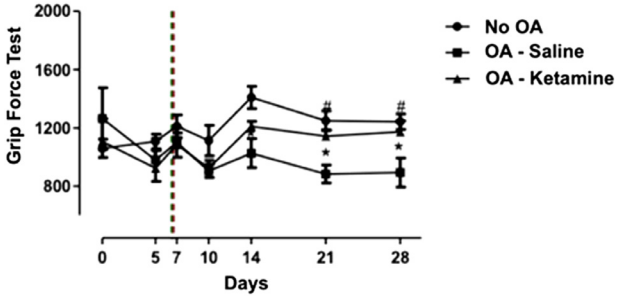

Figure 3 Grip force assessment in rats treated with S(+)-ketamine (n = 6). The data is presented as the nociceptive paw withdrawal threshold in percentage. Vertical symbols and lines indicate the mean and standard error of the means. ANOVA – Tukey's test was performed ($p < 0.05$). The vertical dashed line signifies the beginning of treatment. *Significant difference between the OA-Saline group and the Non-OA group. °Significant difference between the OA-Ketamine group and the Non-OA group. #Significant difference between the OA-Ketamine group and the OA-Saline group.

Table 1 Grading of synovial membrane inflammation (Mean ± standard deviation).

Groups	T			
	Day 7	Day 14	Day 21	Day 28
Non-OA (n = 6)	1.33 ± 1.3	0.16 ± 0.40	0.83 ± 0.75	0.16 ± 0.40
OA-Saline (n = 6)	3.00 ± 0.89[a]	2.66 ± 0.81[a]	3.16 ± 0.75[a]	2.83 ± 1.16[a]
OA-K (n = 6)	3.16 ± 0.40[a]	2.33 ± 0.51[a]	2.16 ± 0.75	1.83 ± 0.98

[a] $p < 0.05$ in comparison to NO-OA (Kruskal-Wallis Test and post-hoc test Dunn).
OA, Osteoarthritis; K, Ketamine.

Discussion

In this study, we employed an experimental model of MIA-induced osteoarthritis. The choice for MIA was based on its established capacity to induce specific changes that closely resemble those found in OA, such as subchondral bone sclerosis, osteophyte formation, cartilage damage, and alterations in biomarkers like glycosaminoglycans and metalloproteinases.[12,20,22] The articular condition that developed in the animals after induction resulted in a reduction in forced walking scores, with the animals displaying signs of joint discomfort, in line with previous findings by other researchers.[7,14,23] Rats treated with S(+)-ketamine showed improved gait as early as the second week of the

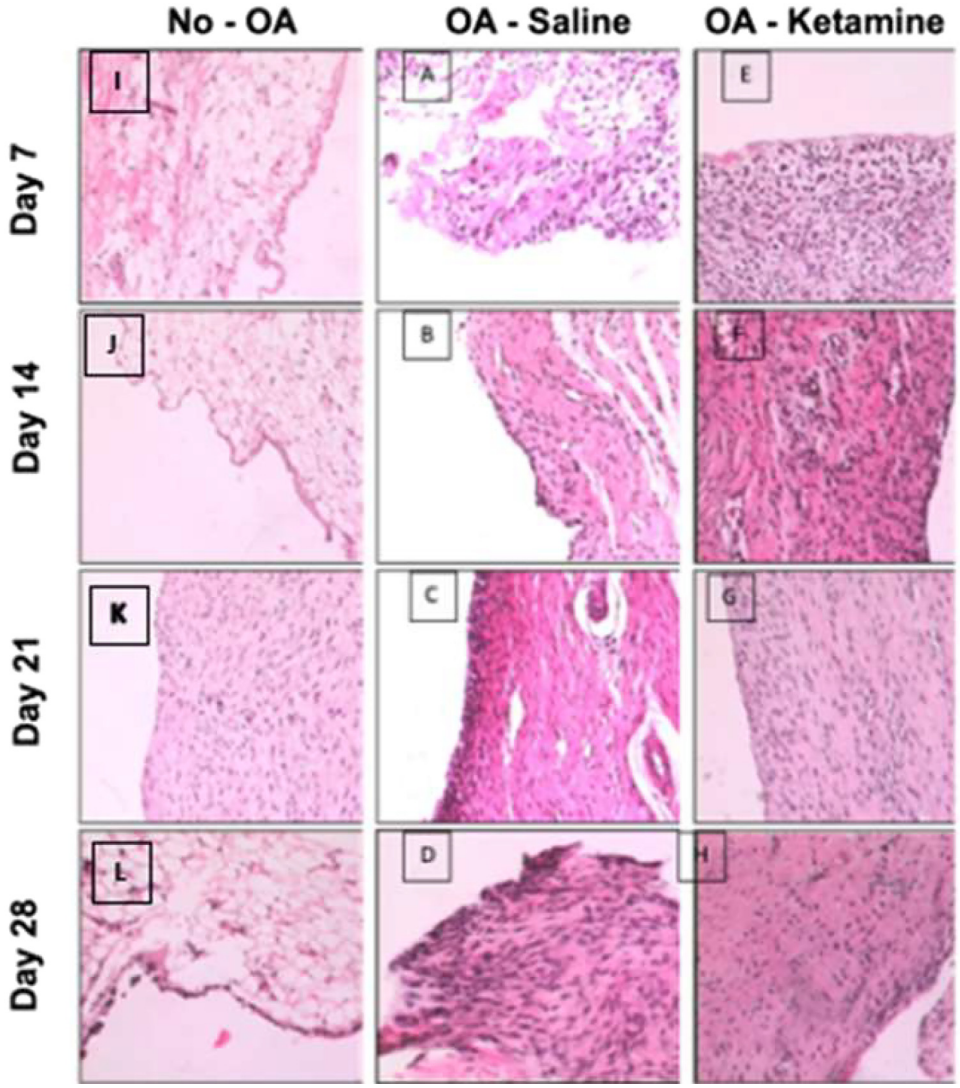

Figure 4 Photomicrograph of the synovial membrane in an experimental model of MIA-induced osteoarthritis. OA-Saline Group (A to D), OA-Ketamine Group (E to H), and NON-OA Group (I to L) stained with hematoxylin and eosin. Notable changes in D show synovial cell proliferation, subsynovial tissue growth, and inflammatory cell infiltration, classified as Grade 4. Grade 0 inflammation score is observed in L, while a Grade 3 inflammation score is seen in C. Magnification: 100 ×.

experiment. Regarding joint discomfort, S(+)-ketamine ameliorated the weight distribution deficit, and by the 14th day, no significant difference was observed between the OA-Ketamine and Non-OA groups.

Moreover, in terms of behavioral assessment, this study demonstrated that MIA injection induced both allodynia and mechanical hyperalgesia. Treatment with S(+)-ketamine effectively reduced the intensity of both allodynia and hyperalgesia until the end of the experiment. MIA injection was observed to decline grip force OR MIA injection led to a decline in grip force from the second week until the conclusion of the study in the saline-treated group, indicating a potential decrease in muscle strength. This finding aligns with those reported in other studies.[19,24] Conversely, S(+)-ketamine resulted in an increase in grip force, possibly attributed to pain relief and subsequent enhanced usage of the affected paw.

The significant differences observed between the groups treated with S(+)-ketamine and saline in behavioral tests can be attributed to NMDAr antagonism. These agents have demonstrated potential in blocking or preventing hypersensitivity states.[2,25] NMDAr antagonists have already proven effective in reducing chronic pain and preventing hyperalgesic phenomena. For instance, a study using MgSO4, known as an NMDAr blocker, in an animal model of OA observed effects on disease progression, including reduced chondrocyte apoptosis and decreased nociception. This study also investigated the behavior of the NR1 receptor, a subtype of NMDAr, on chondrocyte membranes, revealing a decrease in receptor expression, indicating potential prevention of articular cartilage damage.[20] Another study examining NMDAr expression in normal human chondrocytes affected by OA concluded that NR1, NR2A, and NR2B receptors were present in OA-affected human chondrocytes, with NR2B absent in normal chondrocytes. Furthermore, this study demonstrated the blocking of these receptors by NMDAr antagonists.[17]

S(+)-ketamine exhibits a high affinity for NMDAr with NR1/NR2A and NR1/NR2B subunit composition.[26] Its greater affinity (fourfold) for the receptor results in superior analgesic potency. Studies in rats and mice have demonstrated that S(+)-ketamine possesses approximately threefold greater analgesic potency than its isomer and twice the potency of the racemic mixture.[11,27] In our study, we opted for a low dose of S(+)-ketamine (0.5 $mg.kg^{-1}$), in contrast to the doses used in a similar study (12 and 24 $mg.kg^{-1}$) involving a racemic mixture.[7] Despite the differences in dosing between the two studies, behavioral assessment data indicated a reduction in hyperalgesia and mechanical allodynia, as well as an improved gait pattern, suggesting effective pain control. These findings support the idea that low doses of intra-articular (IA) S(+)-ketamine could provide analgesic benefits.

In another study, intraperitoneal administration of S(+)-ketamine was employed to evaluate its antiallodynic effect in conjunction with ketamine and electroacupuncture in a neuropathic pain model. The authors concluded that ketamine injection reduced mechanical allodynia, except at low doses (1 $mg.kg^{-1}$).[28] In our experiment, using a lower dose (0.5 $mg.kg^{-1}$) and an alternative route of administration, the drug effectively alleviated painful behavior within 6 hours of injection.

Our study also included a histopathological analysis to assess synovial membrane inflammation at different time points. However, we found no significant difference between the S(+)-ketamine and saline-treated groups at any time, which contrasts with the findings of two other studies — one conducted in mice[7] and another in rabbits.[8] These studies differed from ours in using racemic mixtures and higher doses of ketamine. Both studies demonstrated dose-dependent effects of ketamine in reversing histopathological changes associated with OA. In the mouse study, which utilized an MIA-induced OA model, histopathological findings were reversed only with a 24 $mg.kg^{-1}$ dose of racemic ketamine — 48 times higher than the dosage in our study.[7] The rabbit study employed a different OA induction model involving immobilization with plaster bandages, resulting in fewer inflammatory cells, and reduced pathological changes with increasing ketamine dosage.[8] These results suggest that higher doses of S(+)-ketamine may have an impact on histopathological findings related to OA.

One of the limitations of this study is the absence of a direct investigation into the mechanisms underlying the observed improvements in behavioral test responses. Therefore, future studies should consider conducting synovial lavage and collecting articular cartilage samples to measure cytokine levels (both anti-inflammatory and pro-inflammatory), nitric oxide levels, receptor expression, and other relevant factors.

Conclusions

In summary, low doses of IA S(+)-ketamine effectively alleviated painful behavior in rats following MIA-induced OA, as evidenced by improvements in behavioral assessments. However, it is important to note that the reversal of histopathological changes in the synovial membrane of the studied joint was not achieved.

Data access

The study data is available upon request to the corresponding author. For inquiries or to request access to the data, please contact corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used CHAT GTP in order to translate and for language improvement. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare no conflicts of interest.

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