

Possible benefit of intra- articular ozone in advanced osteonecrosis of the knee: two case reports

Posible beneficio del ozono intraarticular en la osteonecrosis avanzada de la rodilla: informe de dos casos

Marcos Edgar Fernández-Cuadros¹ , Olga Susana Pérez-Moro¹, Javier Rodríguez de Cía², María Jesús Albaladejo-Florín¹

1. Servicio de Rehabilitación y Medicina Física, Hospital Universitario Santa Cristina, Madrid, Spain.

2. Servicio de Laboratorio Clínico, Hospital Universitario Santa Cristina, Madrid, Spain

Corresponding author

Marcos Fernández-Cuadros

E-mail: marcosfec@hotmail.com

marcosedgar.fernandez@salud.madrid.org

Received: 27 - II - 2023

Accepted: 24 - IV - 2023

doi: 10.3306/AJHS.2023.38.04.170

Abstract

The knee is the second most common site of osteonecrosis (ON) after the hip. Three different entities are described: a) spontaneous ON; b) secondary ON; c) post-arthroscopy ON. In spontaneous ON the etiology is attributed to subchondral insufficiency fractures and to avascular necrosis due to ischemic events. Diagnosis is based on clinical and radiological basis (radiography, bone scan scintigraphy and MRI). Koshino's radiological classification grades severity and guides in the management. Conservative management includes protected weight bearing, drugs (NSAIDs, bisphosphonates, D vitamin, calcium, prostaglandin I-2, corticosteroids, hyaluronic acid), physiotherapy (laser, pulsed electromagnetic fields), and hyperbaric oxygen therapy. Surgical treatment is deserved for advanced stages or if conservative treatment failed. In pre-collapse Stage, joint preserving procedures are expected; on the contrary, in subchondral collapse stages, joint arthroplasty is required. We present for the first time in literature the beneficial effect of intra articular ozone in the management of two cases of advanced ON of the knee.

Keywords: ozone, osteonecrosis of the knee, treatment.

Resumen

La rodilla es la segunda localización más frecuente de la osteonecrosis (ON) después de la cadera. Se describen tres entidades diferentes: a) la ON espontánea; b) la ON secundaria; c) la ON post-artroscopia. En la ON espontánea la etiología se atribuye a las fracturas por insuficiencia subcondral y a la necrosis avascular debida a eventos isquémicos. El diagnóstico se basa en la clínica y la radiología (radiografía, gammagrafía ósea y resonancia magnética). La clasificación radiológica de Koshino califica la gravedad y orienta el tratamiento. El tratamiento conservador incluye la protección del peso, fármacos (AINE, bifosfonatos, vitamina D, calcio, prostaglandina I-2, corticosteroides, ácido hialurónico), fisioterapia (láser, campos electromagnéticos pulsados) y oxigenoterapia hiperbárica. El tratamiento quirúrgico se merece para los estadios avanzados o si ha fracasado el tratamiento conservador. En el estadio precolapso, se esperan procedimientos de preservación articular; por el contrario, en los estadios de colapso subcondral, se requiere una artroplastia articular. Presentamos por primera vez en la literatura el efecto beneficioso del ozono intraarticular en el manejo de dos casos de ON avanzada de rodilla.

Palabras clave: ozono, osteonecrosis de rodilla, tratamiento.

Introduction

Osteonecrosis (ON) of the knee is a progressive disease that leads to subchondral collapse and finally disabling knee osteoarthritis (OA)¹. It was for the first time described in 1968 by Ahlbäck et al². The knee is the second most affected site after the hip³.

Knee ON has been recently classified in three entities: 1) spontaneous ON, the most common type with an incidence of 3.4% in people over 50 years and 9.4% in those over 65; 2) secondary ON affects younger patients, in multiple and bilateral joints, and it is related to alcohol

abuse, tobacco, corticosteroids, sickle cell disease and myeloproliferative disorders; 3) post arthroscopy ON, a rare condition affecting 4% of all arthroscopies mainly due to meniscopathies³.

The etiology of ON of the knee is unknown, although 2 theories are postulated. The vascular insufficiency theory is based on the difference in blood supply between medial and lateral condyles. The traumatic theory states that ON is in reality the result of subchondral insufficiency fractures⁴.

Koshino in 1979 classified ON in four stages: Stage I is normal. Stage II shows radiolucent oval area in subchondral region or flattening of medial femoral condyle (MFC). Stage III depicts an sclerotic halo over radiolucent area and “crescent sign” is observed. Stage IV shows collapse of subchondral bone and osteophytes⁵.

Prognostic factors for knee ON are based on Koshino’s classification and on size of lesion. Lesions inferior to 3.5 cm² tend to regress without surgical intervention. On the contrary, lesions greater than 5 cm² will lead to condyle collapse⁶. Lotke states that lesions involving more than 50% of condylar surface will require arthroplasty⁷.

Di Caprio has stated an algorithm depending on the size of lesion and where collapse is present or not into three categories: a) Non-operative treatment (protected weight bearing, NSAIDs, bisphosphonates, hyperbaric oxygen therapy, pulsed electromagnetic fields); b) joint preserving techniques at pre-collapse stage (arthroscopic debridement, retrograde or anterograde drilling, core decompression, bone grafting, high tibial osteotomy); c) Replacement at collapse stage (osteochondral autografts or allografts, unicompartmental knee arthroplasty [UKA] or total knee arthroplasty [TKA]). This algorithm also applies for post arthroscopy ON but the decision is made on early or late diagnosis (more than 6 months)³. Lair et al also considers Laser, Vitamin D and Calcium, injections of corticosteroids or hyaluronic acid and physiotherapy as conservative treatment⁸. Karim also suggests prostaglandin I₂ as conservative treatment⁹.

In the case of ON of the femoral head, there are two case reports (Iliakis et al and Yildizgorem et al)^{10,11} and a case series of 71 patients (An et al) treated by intra articular ozone therapy¹². However, to the best of author’s knowledge, there is no report on the use of intra articular ozone in the management of knee ON.

Recently, our study group led by Fernández-Cuadros et al has observed symptomatic and disease modifying effect of ozone in osteoarthritis (OA) of the knee in a case report¹³ and in a case series of 115 patients¹⁴, evaluating clinical, biochemical, and radiological variables.

Moreover, in another series of 65 knee OA patients, an improvement of anabolic IGF-1 and a decrease of anti-inflammatory cytokine IL-6 were observed after ozone treatment confirming anabolic and anti-inflammatory properties of ozone in knee OA¹³.

The objective of the present study is to postulate the possible benefit of intra articular ozone in the management of advanced ON of the knee (Koshino’s Stage III-IV) in two females cases and to report for the first time in literature.

Case report

We present two female cases with ON of the knee Stage III on Koshino’s classification treated successfully by intra articular ozone, evaluated by clinical, biochemical and radiological variables.

Case 1: Case 1 is an 83 years old female with ON of the medial femoral condyle (MFC) of the right knee, Stage III. The patient was previously operated in the left knee 10 months ago (TKA). Symptoms begun as acute onset of pain on the medial aspect of the knee. The patient is independent for activities of daily life and is capable of walking only with the help of a cane. She uses paracetamol on demand as a pain killer. Patient was referred to Rehabilitation Department for conservative treatment because she refused to get a TKA of the right knee.

On anamnesis, the patient referred pain (7/10), rigidity (5/8) and function impairment (55/68) as stated by WOMAC scale (Western Ontario and Mc master Index for OA). We explained the properties of ozone highlighting its symptomatic and disease modifying effects, and patient accepted and signed informed consent. We performed clinical, biochemical and radiological evaluation before and after ozone treatment (evaluations at every cycle of ozone). Ozone treatment consisted on 4 sessions of intra articular ozone, 20 mL of 5% ozone at a 20 µg/mL concentration on the lateral aspect of suprapatellar knee.

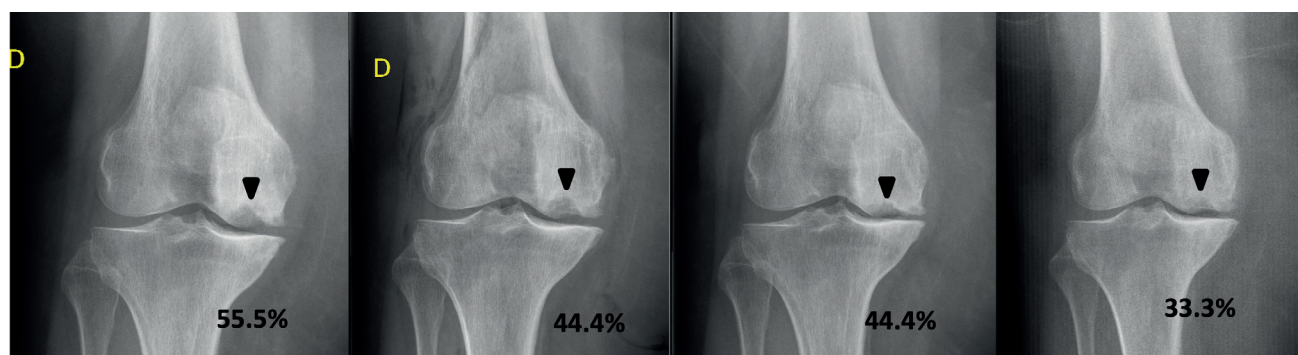
Patient was infiltrated in 6 cycles (4 sessions each cycle), on November 2019, February 2020, October 2020, may 2021, November 2021 and May 2022. We registered clinical and biochemical improvement on the first 4th cycles and radiographies from the beginning to the end of treatment (**Table I** and **figure 1**). There is a clear benefit of ozone treatment in terms of clinical and biochemical variables observed after each cycle; and a radiological improvement from the 1st to 6th cycle after ozone intra articular infiltrations (**Table I** and **Figure 1**). Pain has been reduced in each cycle and function has also improved in the same way.

Table 1: Clinical, biochemical and radiological improvement before and after ozone therapy from cycle to cycle in both case reports.

Variable	Case 1		Case 2	
	Pre-Ozone	Post-ozone	Pre-Ozone	Post-ozone
Clinical				
VAS 1° (1-10)	7	5	8	4
VAS 2° (1-10)	7	5	3	0
VAS 3° (1-10)	7	3		
VAS 4° (1-10)	5	3		
WOMAC Rigidity 1° (0-8)	5	4	5	3
WOMAC Rigidity 2° (0-8)	5	4	2	0
WOMAC Rigidity 3° (0-8)	5	3		
WOMAC Rigidity 4° (0-8)	4	3		
WOMAC Function 1° (0-68)	55	50	60	40
WOMAC Function 2° (0-68)	55	50	35	20
WOMAC Function 3° (0-68)	55	40		
WOMAC Function 4° (0-68)	40	30		
Biochemical				
CRP 1° (mg/mL)	0.58	0.23	0.5	0.4
CRP 2° (mg/mL)	0.2	0.1	1.82	0.52
CRP 3° (mg/mL)	0.7	0.3		
CRP 4° (mg/mL)	0.15	0.16		
ESR 1° (mL/hour)	17	17	27	13
ESR 2° (mL/hour)	14	13	28	20
ESR 3° (mL/hour)	24	24		
ESR 4° (mL/hour)	15	6		
Uric Acid 1° (mg/dL)	6.2	4.7	6.6	5.4
Uric Acid 2° (mg/dL)	5	4.7	5.4	5.3
Uric Acid 3° (mg/dL)	6.1	5.5		
Uric Acid 4° (mg/dL)	5.2	5.0		
IL-6 1° (pg/mL)	8.41	6.01	1.15	0.83
IL-6 2° (pg/mL)	2.09	2.07		
IL-6 3° (pg/mL)	2.3	2.0		
IGF-1 1° (ng/mL)	114.7	136.4	63.47	102.0
IGF-1 2° (ng/mL)	109.9	138.6		
Radiological				
Surface involvement 1° (%)		55.5		50
Surface involvement 2° (%)		44.4		41.6
Surface involvement 3° (%)		44.4		33.3
Surface involvement 4° (%)		33.3		

VAS, visual analogue scale. WOMAC, Western Ontario and Mc Master Index for Osteoarthritis. ESR, erythrocyte sedimentation rate. IL-6, Interleukin 6. IGF-1, Insulin growing factor 1.

Figure 1: Case 1 after 6 cycles of intra articular ozone infiltrations. Radiographies were performed on October 2019; December 2020; November 2021 and May 2022. On each radiography, surface involvement of osteonecrosis of the medial femoral condyle is expressed in percentage.



Case 2: Case 2 is a 70 years old female with ON of the MFC of the left knee, Stage III (Koshino’s classification). Patient reported acute onset of pain on medial aspect of the knee and secondary pain on left trochanter because of antalgic walking. Patient was referred to Rehabilitation Department for conservative treatment. At that time, she was candidate for UKA.

At Rehabilitation Department, patient was prescribed pulsed electromagnetic fields (PEMFs) on the left knee

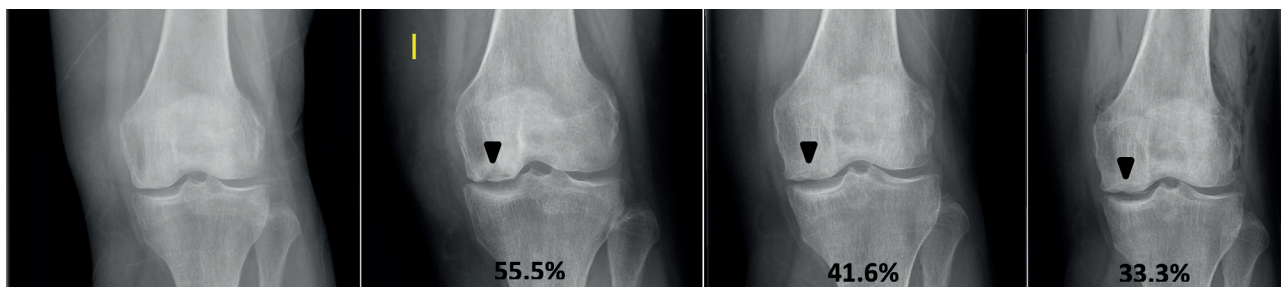
and transcutaneous electrical nerve stimulation (TENS) on left trochanter. After 10 sessions (5 sessions/week) and no improvement on pain and gait, she was offered intra articular ozone therapy because of its symptomatic and disease modifying effect on knee OA.

After acceptance and signed informed consent, patient received 2 cycles (4 sessions each) of 20 mL of 5% ozone at a 20 µg/mL concentration. Clinical symptoms (pain, function and rigidity evaluated by WOMAC scale),

biochemical (PCR, ESR, Uric Acid, IL-6 and IGF-1) and radiological variables were evaluated before and after each cycle (Table 1 and Figure 2). Patient was infiltrated on

October 2021 (first cycle) and on April 2022 (second cycle). Symptoms and gait improved to the point that a cane was no longer used for walking, and pain disappeared at all.

Figure 2: Case 2 after 2 cycles of intra-articular ozone infiltrations. Radiographies were performed on April 2019; September 2020; May 2021 and April 2022. On each radiography, surface involvement of osteonecrosis of the medial femoral condyle is expressed in percentage.



Discussion

To the best of author's knowledge, these are the first two cases of severe ON of the MFC of the knee treated successfully by intra-articular ozone and evaluated by clinical, biochemical and radiological variables.

Ahlbäck in 1968 was the first to describe spontaneous ON of the knee. He described the entity as acute onset of pain typically presented in the MFC, affecting more commonly females and older than 60 years². This is in accordance with our two cases, females of 70 and 83 years with acute onset of pain on the medial aspect of the knee. The presentation is usually in the medial condyle more than lateral one.

In the case of secondary ON of the knee, the presentation is in people younger than 45 years, could be multilateral and is more frequent in hips than in knees¹. Risk factors include alcohol abuse, coagulopathies, Caisson's disease, chemotherapy, corticosteroids, Cushing's Syndrome, diabetes, familial thrombophilia, Gaucher's disease, gout, hyperthyroidism, irritable bowel disease, liver disease, organ transplantation, pancreatitis, pregnancy, radiation, renal disease, sickle cell disease and other hemoglobinopathies, smoking, systemic lupus erythematosus and tumors³.

Another form is post-arthroscopy ON of the knee. This is the rarest form of ON of the knee with a prevalence of 4% of all arthroscopies. Meniscopathy is present in 87% of cases. Onset is usually after 6 weeks of the procedure³. None of our cases were treated by arthroscopy procedures before onset of pain.

The etiology of ON is thought to be vascular and is characterized by loss of blood flow circulation¹. Since ozone is believed to improve rheology of erythrocytes and to favor delivery of oxygen to tissues (by formation of 2,3 DPG which displaces the curve of dissociation of hemoglobin to the right)¹⁵. This fact would explain the clinical and radiological improvement observed in

our cases. Another theory for the explanation of ON presentation is that mechanical factors would lead to subchondral insufficiency fractures³. Since we have previously postulated and lately demonstrated that Ozone could stimulate stem cells, chondrocytes and growth factors (TGF- β and IGF-1) in knee OA¹³⁻¹⁴, and we have observed improvement in minimal joint space in knee OA patients¹⁴, we believe that these properties have been responsible for the radiological improvement in knee ON. In fact, case 1 reduced surface ON lesion from 55.5% to 33.3% and case 2 ameliorated ON lesion from 50% to 33.3%.

Prognosis of ON of the knee is based on size of the lesion (3.5 cm² vs 5 cm²), surface involvement of lesion (50%) and Kashino's classification (Stage I-II vs III-IV). Most algorithms state conservative treatment in lesions inferior to 3.5 cm², surface involvement lower than 50% or Kashino's Stage I-II. On the contrary, surgical treatment is proposed if lesion is greater than 5 cm², superior than 50% surface involvement or Stage III-IV. It depends of pre-collapse to perform arthroscopic procedures or high tibial osteotomy; or collapse Stage to perform osteochondral autografts or UKA or TKA³.

Intra-articular infiltrations of hyaluronic acid, corticosteroids⁸, stem cells or platelet-rich plasma¹¹ are considered as conservative treatment for the management of early Stages (I-II) of knee ON. The importance of the study is that for the first time in literature, we report the benefit of intra-articular ozone in the management of advanced knee ON (Stages III-IV) where only surgical procedures are considered and it is supposed that intra-articular infiltrations have no place on such advanced stages.

In a very recent article, Spassim et al, in a rat model of knee OA, have demonstrated that 60 daily sessions of intra-articular ozone (at 5 and 10 μ g/mL concentration) could delay the degeneration of the articular cartilage evidenced clinically, radiologically and histologically¹⁶. These findings would explain the radiological improvement observed in our two case reports.

There are only three publications on the benefit of intra articular ozone for the management of hip ON. Iliakis et al have stated that in a 43 years old female with ON of the left hip, 7 sessions of intra articular ozone (5 mL at a 40 µg/mL concentration) improved clinical and radiological status¹⁰. Yildizgoren reported that in a 45 years old male with bilateral hip ON secondary to corticosteroids use (for treatment of Hodgkin's lymphoma), after 5 sessions (1/week) of intra articular ozone (15 mL at increasing doses of 15, 20 and 25 µg/mL concentration) the patient ameliorated pain (VAS from 7 to 2) and improved walking distance (from 100 to 1000 meters)¹¹. An et al, in a series of 71 patients with hip ON, observed that 3 cycles of 10 sessions of intra articular ozone (5 sessions/week) every three months (30 mL at 30 µg/mL concentration) improved pain (VAS scale), Harris Hip Score and bone marrow edema. Ozone also delayed total hip arthroplasty at a 30-months follow-up period².

Conclusion

Based on two case reports, intra articular ozone could improve clinical, biochemical and radiological variables in patients with advanced ON of the knee. It is necessary to perform a study with a greater sample to confirm the promising benefit observed in this report.

References

- Mont MA, Marker DR, Zywił MG, Carrino JA. Osteonecrosis of the knee and related conditions. *J Am Acad Orthop Surg*. 2011 Aug;19(8):482-94. doi: 10.5435/00124635-201108000-00004.
- Ahlbäck S, Bauer GC, Böhne WH. Spontaneous osteonecrosis of the knee. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 1968; 11(6):705-33.
- Di Caprio F, Meringolo R, Navarra MA, Mosca M, Ponziani L. Postarthroscopy Osteonecrosis of the Knee: Current Concepts. *Joints*. 2017 Nov 6;5(4):229-236. doi: 10.1055/s-0037-1608666.
- Alexa, O., Cionca, D., Albetar, S., & Veliceasa, B. (2015). Spontaneous Osteonecrosis of the Medial Femoral Condyle: Case Report. *chirurgie*, 10(4), 291-3.
- Koshino T, Okamoto R, Takamura K, Tsuchiya K. Arthroscopy in spontaneous osteonecrosis of the knee. *The Orthopedic Clinics of North America* 1979; 10(3):609-18.
- Sibilska A, Góralczyk A, Hermanowicz K, Malinowski K. Spontaneous osteonecrosis of the knee: what do we know so far? A literature review. *Int Orthop*. 2020 Jun;44(6):1063-1069. doi: 10.1007/s00264-020-04536-7.
- Lotke PA, Abend JA, Ecker ML. The treatment of osteonecrosis of the medial femoral condyle. *Clinical Orthopaedics and Related Research* 1982;171:109-16.
- Lair J, Fink C, Csapo R. Spontaneous Osteonecrosis of the Knee: a Systematic Review of Conservative Treatment Approaches. *Research Square*, 2021. DOI: 10.21203/rs.3.rs-239294/v1.
- Karim AR, Cherian JJ, Jauregui JJ, Pierce T, Mont MA. Osteonecrosis of the knee: review. *Ann Transl Med*. 2015 Jan;3(1):6. doi: 10.3978/j.issn.2305-5839.2014.11.13.
- Iliakis E, Bonetti M, Iliakis A. Osteonecrosis of the femoral head: Could oxygen-ozone therapy become a treatment option?. *Journal of Ozone Therapy* 2015; 1(1):3-7.
- Yildizgören MT, OĞUZ H. Ultrasound-Guided Intra-Articular Ozone Injection as a Therapeutic Option for Hip Osteonecrosis. *Journal of Physical Medicine & Rehabilitation Sciences/Fiziksel Tıp ve Rehabilitasyon Bilimleri Dergisi* 2020; 23(3).
- An JX, Wu GP, Niu K, Wei YP, Liu H, Gao XY, Wu JP, Wang Y, Renz H, Williams JP. Treatment of Femoral Head Osteonecrosis with Ozone Therapy: Pilot Trial of a New Therapeutic Approach. *Pain Physician*. 2022 Jan;25(1):E43-E54.
- Fernández-Cuadros ME, Pérez-Moro OS, Albaladejo-Florín MJ, Álava-Rabasa S. Symptomatic (Pain and Inflammation) and Disease-Modifying Effect (Minimal Joint Space) of Intra-articular Ozone (O₂-O₃) in Osteoarthritis of the Knee: a Clinical Case. *SN Comprehensive Clinical Medicine* 2019;1(10):817-21.
- Fernández-Cuadros ME, Pérez-Moro O, Albaladejo-Florín MJ, Álava-Rabasa S. El ozono intra-articular modula la inflamación, mejora el dolor, la rigidez, la función y tiene un efecto anabólico sobre la artrosis de rodilla: estudio cuasi-experimental prospectivo tipo antes-después, 115 pacientes. *Revista de la Sociedad Española del Dolor* 2020; 27(2):78-88.
- Fernández-Cuadros ME, Albaladejo-Florín MJ, Peña-Lora D, Álava-Rabasa S, Pérez-Moro OS. Ozone (O₃) and SARS-CoV-2: physiological bases and their therapeutic possibilities according to COVID-19 evolutionary stage. *SN Comprehensive Clinical Medicine* 2020; 2(8):1094-102.
- Spasim MR, Dos Santos RT, Rossato-Grando LG, Cardoso L, da Silva JS, de Souza SO, et al. Intra-articular ozone slows down the process of degeneration of articular cartilage in the knees of rats with osteoarthritis. *The Knee* 2022; 35: 114-23.

Acknowledgments

Saturnino Díaz Trujillo, librarian at Hospital Universitario Santa Cristina, Madrid, is acknowledged for the bibliographic search to carry out this study.

Compliance with ethical standards

Dr. Jose Gabriel Perez Karduss is acknowledged for the statistical analysis.

Funding

For the elaboration of the manuscript authors received no financial funding.

Conflicts of interest

The authors declare no conflict of interest.

Ethics approval

The case report has been approved by the Ethical Committee of the Hospital.

Consent to participate

For the application of this treatment, patients signed an informed consent.

Consent for publication

For case report publication, patients signed an informed consent.