U.PORTO

FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2017/2018

Tânia José Silva Costa

Ozonoterapia na dor lombar. Revisão Sistemática

Ozone therapy for low back pain. A systematic review

março, 2018

Tânia José Silva Costa

Ozonoterapia na dor lombar. Revisão sistemática

Ozone therapy for low back pain. A systematic review

Mestrado Integrado em Medicina

Área: Ortopedia

Tipologia:Monografia

Trabalho efetuado sob a Orientação de:

Doutor Nuno Silva de Morais Neves

Trabalho organizado de acordo com as normas da revista:

Acta Reumatológica Portuguesa

março, 2018

FMUP

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Tânia José Silva Costa, abaixo assinado, nº mecanográfico 201008283, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 22/03/2018

Assinatura conforme cartão de identificação:

Tânia José Silva Costa

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Tânia José Silva Costa

NÚMERO DE ESTUDANTE | E-MAIL

201008283 | taniacosta_24@hotmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Ortopedia

TÍTULO MONOGRAFIA

Ozone Therapy for Low Back Pain. A systematic review

ORIENTADOR

Nuno Silva de Morais Neves

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 22/03/2018

Assinatura conforme cartão de identificação: Tânia José Silva Costa

Title

Ozone therapy for low back pain. A systematic review

Authors and affiliation

Tânia S. Costa[1], Daniela Linhares[2,3], Manuel Ribeiro da Silva[3,4,5,6], Nuno Neves[3,4,5,6]

[1] FMUP – Faculty of Medicine, University of Porto

[2]MEDCIDS – Faculty of Medicine, University of Porto

[3]Orthopedic Department, Centro Hospitalar de São João, Porto

[4]Surgery Department – Faculty of Medicine, University of Porto

[5]CUF Porto Hospital

[6]I3S – Instituto para a Investigação e Inovação em Saúde

Corresponding author information

Nuno Neves

Serviço de Ortopedia

Centro Hospitalar São João

Alameda Professor Hernâni Monteiro

4200-319 Porto

Phone: (+351) 934142782

E-mail: nsmneves@gmail.com

ABSTRACT

Background: Low back pain associated with lumbar disc herniation is common in the general population, with evident repercussion in quality of life and a significant economic burden. Patients refractory to conservative treatment seek additional treatment and minimally invasive interventions were proposed as valid options. Ozone therapy has been suggested as an alternative due to its potential analgesic and anti-inflammatory effect.

Objective: This systematic review aims to investigate the effectiveness and safety of ozone therapy for low back pain in patients with lumbar disc herniation.

Material and Methods: A systematic search was performed in Pubmed and Scopus, followed by a three-step selection process. Data was processed by 2 independent reviewers and information was gathered based in pre-defined variables. Only articles performed in humans; original and English written; on treatment with ozone; comparing the result of ozone therapy (experimental group) with another non-ozone intervention (control group); and on patients with lumbar pain and disc hernia, were included.

Results: From 439 references retrieved after duplicates removal, inclusion and exclusion criteria were applied, and 7 studies were included in the final revision. One article compared treatment with ozone versus placebo, one ozone and global postural re-education versus global postural re-education alone, two the combination of ozone with steroid versus steroid alone, two ozone versus steroid and one ozone versus micro-discectomy. All but the study comparing ozone application with micro-discectomy, showed similar or better results in the experimental group. Only three studies evaluated the presence of side effects. In two papers no complication was reported, and in the other, a low percentage of adverse effects was observed, not significantly different between the two study groups.

Conclusions: Only a small number of poor quality studies on ozone effect in low back pain and disc herniation were available for inclusion in our review. Nevertheless, these reported an improvement in pain and functional scores with its application. Complications, mostly minor, but potentially serious are underreported. Additional studies with adequate and consistent methodologies are needed before the role of ozone can be established in the management of low back pain.

Keywords: low back pain; lumbar disc hernia; oxygen-ozone therapy; ozone injection

INTRODUTION

Low back pain (LBP) is a very common disorder with significant impact on patients' clinical status, and relevant socioeconomic and public health consequences[1]. The prevalence is estimated at 22-65% per year, and up to 80% of the population presents mild to severe LBP at some point in life[1]. In approximately 60-80% of cases, no specific cause is diagnosed, and the pain is attributed to muscle or ligament tension, and in only 5-15% to degenerative causes and disc injuries. Symptomatic disc herniation is a degenerative disease of the intervertebral disc that presents with low back pain, sciatica or lumbar compressive radiculopathy with functional limitations[1]. Studies on the natural history of disc herniation show that most of the associated symptoms decrease significantly after conservative treatment[2]. Lumbar disc herniations (LDH) are also frequently detected in asymptomatic individuals who undergo additional diagnostic tests for other medical complaints, and its prevalence is estimated at 57%[3]. LDH is therefore a relatively common condition with a favorable prognosis in most cases[4]. Still LDH is the most frequent indication for surgery of the spine. Although good results can be expected, the reoperation rate is between 7-9% at 2 years and increases to 10-25% at 10 years postoperatively[5]. Up to 20% of patients maintain pain after surgery, and recurrences of LDH, as well as adhesion phenomena, post-surgical scars and fibrosis, may require new surgical intervention, which in turn can produce acute symptomatology with instability of the spine[6, 7]. Therefore, different minimally invasive, well-tolerated and low-cost procedures have been developed to provide good clinical results without the associated drawbacks of surgery[1].

Ozone, the triatomic form of oxygen, is a strong oxidant, capable of inducing several useful biological responses and, eventually, reversing chronic oxidative stresses such as those derived from degenerative processes[8]. Using the ability of ozone to cleavage proteoglycans and neutralize the negative charge of sulfate side chains, water retention can be diminished, resulting in a reduction of the volume of the hernia[5].

Intradiscal ozone injection was first proposed in Italy in the 1980s as a treatment for herniated disc[5]. A mixture of ozone and oxygen (O2O3) can be injected directly in the disc or indirectly in the paravertebral muscles aiming to reduce herniation, relieving nerve root compression, with potential analgesic and anti-inflammatory effects[8, 9]. It is currently used in many European, Asian ant South American countries as a minimally invasive approach to treat LDH refractory to conservative treatment, or for those with contraindications for surgery[3].

Despite its increasing popularity, the scientific data regarding both its effectiveness and safety is scarce, and adequately performed randomized controlled trials (RCTs), and meta-analysis are definitely needed[8, 10, 11].

The aim of this systematic review is to investigate the effectiveness and safety of ozone therapy for low back pain and lumbar disc herniation.

MATERIAL AND METHODS

A systematic search was conducted in Pubmed and Scopus, using as a query, a combination of ("ozone therapy" or "ozone" or "ozone nucleolysis") and ("chronic low back pain" or "back pain" or "pain" or "spine" or "vertebra" or "column" or "disc" or "disc hernia"). Subsequently a selection process was carried out in three stages. The data was processed by two independent reviewers and the information was collected based on pre-defined variables. In the first step, titles and abstracts were selected, and articles proceeded to the second stage after the inclusion by at least one reviewer. Within the second stage, full-text was evaluated and the disagreements were discussed among reviewers.

Inclusion criteria were: articles performed in humans; original and English written articles; articles on treatment with ozone; articles comparing the result of ozone therapy (experimental group) with another non-ozone intervention (control group); on patients with lumbar pain of degenerative causes. All those whose patients had other known conditions rather than degenerative lumbar changes (i.e. inflammatory or infectious arthritis, neoplastic conditions) were excluded. When the full text was not available, the authors were asked for full text copy. One article was excluded due to unavailability of the full text.

Two comparison groups were previously defined based in data gathered from each individual article, an experimental group, which received ozone, and a control group that receives the same treatment without ozone. Data on demographics, diagnosis, treatment and ozone application and clinical and/or radiologic assessments was collected.

When available, data on significance of each study was also pooled, with a statistically significant value defined as $p < 0.05$. This review was performed based on Items Preferred Reports for Systematic Reviews and Guidance Indicators for Meta-Analyzes (PRISMA)[12]. PRISMA checklist is available on Supplementary File.

RESULTS

From 439 references retrieved after duplicates removal, inclusion and exclusion criteria were applied, and 7 studies were included in the final revision (Table I, Figure 1). Two articles on ozone versus steroid, two on the combination of ozone with steroid versus steroid alone, one on ozone versus a sham procedure, one on ozone versus microdiscectomy, and another one on ozone versus global postural re-education (GPR), and ozone and GPR versus GPR alone. Follow-up times from individual studies ranged from 2 weeks to 5 years. Different injection routes and ozone concentrations were used in the studies included. All performed at least a clinical evaluation such as Visual Analog Scale (VAS) for pain, Oswestry Disability Index (ODI) and McNabb method, and 4 also underwent a complementary assessment with Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI).

Apart from the study comparing ozone application with micro-discectomy, all studies showed similar or better results in the experimental group. In particular, evolution of pain was assessed in all articles, with six reporting a significant decrease in the experimental group in at least one study time. On the other hand, in the two studies that reported on functional assessment, only one observed a significant improvement in some of the clinical scores applied (Table II).

Only three authors reported the incidence of side effects. In two papers no patient from either study group suffered any complication, and in the other, authors stated a low percentage of adverse effects, not significantly different between the two study groups (Table I and II).

DISCUSSION

This systematic review assessed the effectiveness and safety of ozone therapy for low back pain due to lumbar disc herniation. Most articles included showed improved results in both pain and functional status with therapies including ozone when compared to a control ozone-free group. This is in agreement with previous reviews, which showed similar results[10, 11].

Nevertheless, only 7 papers were included in the final synthesis, according to our strict inclusion criteria, and several limitations can be pointed out in these studies. First, different protocols were used in each study, with diverse ozone concentrations and doses, routes of application, and outcome assessment methods. Also, only two groups of two articles had the same generic comparisons, and even these performed with different

methodologies, which precluded a quantitative analysis. All articles assessed evolution and/or resolution of pain complaints, but only 4 with comparable VAS evaluations. Additionally, disc hernia definition was absent from the majority of the included papers, as were the definitions of positive radiological outcomes. Most of the articles did not report on losses to follow-up and their management, on blinding and randomization and/or allocation methods, when applicable.

Two previous systematic reviews are available on ozone application for LBP. One, in Spanish, also pointed out the low quality of the available data[10]. As in this review, the author states that positive results from this procedure were observed in patients with disc hernia, but these were based on inadequately performed studies with lack of standardization of techniques and assessment methodologies. Despite these weaknesses, these results were not very different from those observed with other infiltration techniques, and the conclusion was that better studies are needed to sustain the use of this therapy. The other review recommended ozone treatment in disc herniation[11]. However, this should be interpreted with caution, since only 4 articles with poor methodological approach supported these recommendations.

When compared to a conventional microdiscectomy, ozone therapy failed to demonstrate any additional benefit, especially in extruded herniations, where ozone infiltrations are usually considered less effective or even contraindicated[13]. It has been widely reported that spontaneous improvement of pain and neurologic deficits is common in patients with disc hernia, and that the vast majority are able to return to work within three months from the onset of symptoms, without resorting to surgery[2]. Whether ozone infiltration actually influences the natural history of disc herniation is still a matter of debate.

Ozone therapy is frequently cited as a low risk complication procedure[8]. Accordingly, ozone injections are proposed for patients with contraindications for surgery or as a temporary or exploratory pain relief therapy before surgical procedures[3, 13]. Surprisingly, although ozone is regarded as a potentially toxic agent, very few studies actually report on the complications resulting from this therapy. These are mostly generic side effects: insomnia, itching, papules around the point of infiltration, gastritis, dizziness, tachycardia and hot flushes[11, 14]. Only three of the included references [3, 14, 15] explicitly reported on this. In two of them no complications were demonstrated in either study group, and in the other a low incidence was reported with no differences between groups. Recently, serious infectious events related to ozone infiltration have also been

published[16, 17]. In an observational study of patients undergoing surgery for disc herniation or spinal stenosis, Vanni et al. reported the unexpected discovery of hard adhesions between the contracted root and the dural sac and/or fragmented disc, only in those previously submitted to ozone therapy[18]. This questions the idea of a totally safe procedure that can be attempted before surgery, and guidelines and protocols for its use should be better established.

Ozone use in the medical field is currently not approved either by FDA or EMEA as there are no meta-analysis or multicentric studies to definitely prove its efficacy[16]. Still, it is widely prescribed in various countries of Europe, Asia and South America, and more than 3000 treatments are performed every day in Italy alone[18]. This review further reinforces the need of well-designed studies to provide adequate support for or against ozone treatment recommendations.

This systematic review has some limitations. No quantitative assessment was performed due to the high heterogeneity of data. Also, neither a publication bias, nor a quality assessment were performed. Although one may infer the poor quality of the included studies, this analysis would increase the validity of our conclusions. Nevertheless, it is an appropriate summary of the current evidence available on this topic.

CONCLUSION

Little evidence is available on the effect of ozone injections in patients with low back pain due to lumbar disc herniation. However scarce and of poor quality, the studies gathered reported an improvement in pain and functional scores with its application. Complications, mostly minor, but potentially serious are underreported. Additional studies with adequate and consistent methodologies are needed before the role of ozone can be established in the management of low back pain.

REFERENCES

1. Hashemi M, Poorfarokh M, Mohajerani SA et al. Injection of intradiscal O2-O3 to reduce pain and disability of patients with low back pain due to prolapsed lumbar disk. Anesth Pain Med. Anesth Pain Med. 2014 Nov 21; 4(5):e19206.
2. Casey E. Natural history of radiculopathy. Phys Med Rehabil Clin N Am. 2011 Feb; 22(1):1-5
3. Paoloni M, Di Sante L, Cacchio A et al. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation. Spine 2009; 34: 1337-1344.
4. Bonetti M, Zambello A, Leonardi M, Princiotta C. Herniated disks unchanged over time: Size reduced after oxygen-ozone therapy. Interventional Neuroradiology 2016; 22: 466-472.
5. Buric J, Rigobello L, Hooper D. Five and ten year follow up on intradiscal ozone injection for disc herniation. Int J Spine Surg. Int J Spine Surg. 2014 Dec 1; 8.
6. Li B, Xu XX, Du Y et al. CT-guided chemonucleolysis combined with psoas compartment block in lumbar disc herniation: a randomized controlled study. Pain Medicine 2014; 15: 1470-1476.
7. Brina L. Lumbar disc disease: 10 years of experience in paravertebral infiltration with oxygen-ozone mix. International Journal of Ozone Therapy 2010; 9: 93-95.
8. Bocci V, Borrelli E, Zanardi I, Travagli V. The usefulness of ozone treatment in spinal pain. Drug Des Devel Ther. 2015 May 15; 9: 2677-85.
9. Andreula CF, Simonetti L, Santis F, Agati R, Ricci R, Leonardi M. Minimally invasive oxygen-ozone therapy for lumbar disk herniation. AJNR Am J Neuroradiol 2003; 24: 996-1000.
10. Carmona L. Revisión sistemática: ozonoterapia en enfermedades reumáticas. Reumatol Clin. 2006; 2(3):119-123.
11. Magalhães FNO, Dotta L, Sasse A, Teixeira MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: A systematic review and meta-analysis of randomized controlled trials. Pain Physician 2012; 15: 115-129.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339:b2700.

13. Paradiso R, Alexandre A. The different outcomes of patients with disc herniation treated either by microdiscectomy, or by ozone injection. Acta Neurochir 2005; 92: 139-142.
14. Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM. An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. Functional Neurology 2014; 29(1): 31-39.
15. Gallucci M, Limbucci N, Zugaro L et al. Sciatica: Treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. Radiology 2007; 242: 907-913.
16. Balan C, Schiopu M, Balasa D, Balan C. Ozone therapy – a rare and avoidable source of infectious pathology of the spine. Romanian Neurosurg. 2017; 31(3): 281-288
17. Gazzeri R, Galarza M, Neroni M, Esposito S, Alfieri A. Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine (Phila Pa 1976). 2007; 32(3): E121–E123
18. Vanni D, Galzio R, Kazakova A, Pantalone A, Sparvieri A, Salini V, Magliani V. Intraforaminal ozone therapy and particular side effects: preliminary results and early warning. Acta Neurochir. 2016 May; 158(5): 991-3
19. Zambello A, Fara B, Tabaracci G, Bianchi M. Epidural steroid injection vs paravertebral O2-O3 infiltration for symptomatic herniated disc refractory to conventional treatment: A prospective randomized study. Rivista di Neuroradiologia 2006; 5: 123-127.
20. Bonetti M, Fontana A, Cotticelli B, Volta GD, Guindani M, Leonardi M. Intraforaminal O2-O3 versus periradicular steroidal infiltrations in lower back pain: Randomized controlled study. AJNR Am J Neuroradiol 2005; 26: 996-1000.
21. Perri M, Grattacaso G, di Tunno V et al. T2 shine‐through phenomena in diffusion ‐weighted MR imaging of lumbar discs after oxygen–ozone discolysis: a randomized, double-blind trial with steroid and O2–O3 discolysis versus steroid only. Radiol Med. 2015 Oct; 120(10): 941-50.

Table I. Data from individual studies

ID	Age (mean±SD)	N (E/C)	Gender (M/F)	Experimental Group		Control Group		Clinical Assessment	Other Assessments	Study Times	Side Effects % (E/C)
Zambello, 2006	E: 51±6.1; C: 48±3.2	351 (180/171)	191/160	Ozone	5 mL paravertebral injection (10-20 μg/mL)	Steroid	80mg triamcinolone epidural injection	**Pain:** McNabb method (excelente/good)	NA	3w; 6m	NI
Bonetti, 2005	48	306 (86/80)	128/178	Ozone	3mL intraforaminal injection (25μg/mL)	Steroid	80 mg methylprednisolone periradicular injection	**Pain**: McNabb method (excelente/good)	NA	1w, 3m, 6m	NI
Perri, 2015	E: 44.4±9.5; C: 43.8±11.2	154 (77/77)	NI	Steroid+ Anesthetic + Ozone	Similar to control + 10 mL intradiscal and intraforaminal ozone injection (28 μg/ml)	Steroid + Anesthetic	2-3mL of betamethasone Intraforaminal and epidural injection (4mg/2ml) + 2-3mL ropivacaine 2%	**Pain**: VAS	**MRI** (T2 shine-through effect; DWI signal)	2m, 4m, 6m	NI
Galluci, 2007	E: 48.8±13.6; C: 47.2±11.9	159 (82/77)	88/71	Steroid + Anesthetic + Ozone	Similar to control + 10-14mL intraforaminal and intradiscal ozone injection (28 μg/mL)	Steroid + Anesthetic	2mL triamcinolone intraforaminal and intradiscal injection (40 mg/mL) + 2-4mL ropivacaine 2%	**Functional**: ODI (>20% positive variation)	NA	2w, 3m and 6m	0/0
Paoloni, 2009	18-65[#]	60 (36/24)	28/32	Ozone	20 mL intramuscular paravertebral infiltrations (20 μg/mL) – 15 times	Sham procedure	Sham procedure	**Pain**: VAS, **Functional**: SF-36 Backill, Kellner, Drug assumption	**MRI** (reduction in disc hernia)	2w, 4w, 6w, 3m, 6m	0/0
Paradiso, 2005	30-60[#]	300 (150/150)	152/148	Ozone	Percutaneous discolysis	Micro-discectomy	NI	**Pain**: VAS **Functional**: ODI	**EMG**, **CT/MRI** (reduction in disc hernia)	4-6m, 1y, 3y	NI
Apuzzo, 2014	E: 50.3±13.5 C: 46.1±13.2	546 (109/54)	279/267	Ozone	Ozone: 15 mL intramuscular paravertebral injection (20 μg/mL) (12 biweekly + 10 maintenance sessions)	GPR	Breathing, stretching and proprioception exercises (12 biweekly sessions of + 3 maintenance sessions)	**Pain**: VAS **Functional**: RL-p, SF-36	**MRI** (reduction in disc hernia) Recurrence	1m, 3m	0.9/NI
	E: 50.5±14.2 C: 46.1±13.2	546 (383/54)		Ozone + GPR							1.6/NI

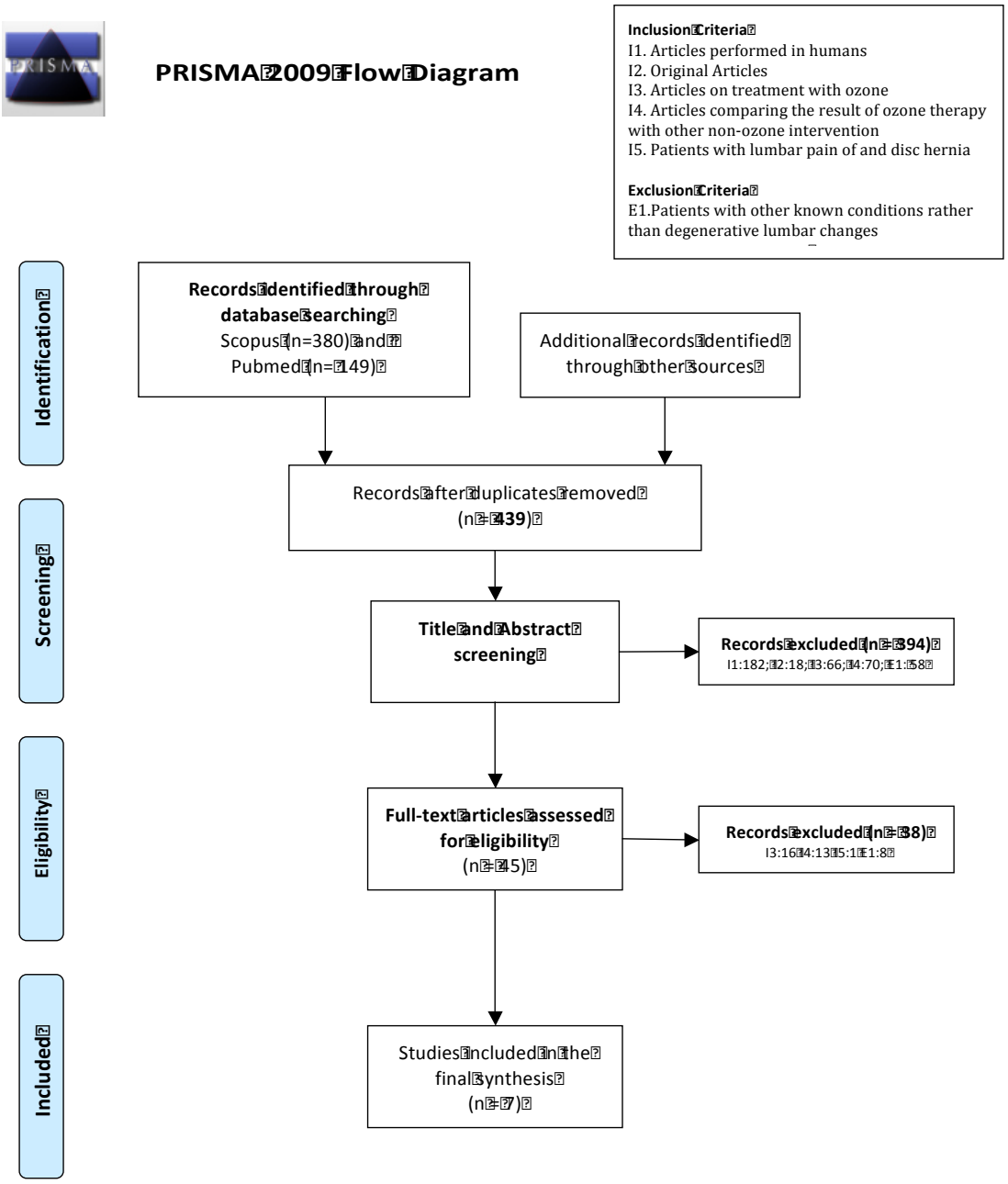
E: Experimental; C: Control; w: weeks; m: months; y: years; NA: Not Assessed; NI: No Information; NC: No Comparison; VAS: Visual Analog Scale; SF-36: Short Form 36 Questionnaire; ODI: Oswestry Disability Index; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; EMG: Electromyogram; GPR: Global Postural Re-education. [#]Min-Ma

Table II. Comparisons between Experimental and Control groups.

ID	Study times	Experimental Group	Control Group	Outcome Assessment			Side Effects
				Pain	Functional	Other	
Zambello, 2006	3w	Ozone: 5 mL (10-20 µg/mL)	Steroid (80mg)	↓*		NA	NI
	6m			↓*			
Bonetti, 2005	1w	Ozone: 3mL (25µg/mL)	Steroid (80 mg)	≈		NA	NI
	3m			≈			
	6m			↓*			
Perri, 2016	2m	Steroid/Anesthetic + Ozone: 10 mL (28 µg/ml)	Steroid (4-6mg) + Anesthetic (2-3mL)	≈		MRI: ≠	NI
	4m			≈			
	6m			↓*			
Galluci, 2007	2w	Steroid/Anesthetic + Ozone: 10-14mL (28 µg/mL)	Steroid (80mg) + Anesthetic (2-4mL)	≈		NI	≈
	3m			≈			
	6m			↓*			
Paoloni, 2009	2w	Ozone: 20 mL (20µg/mL)	Sham Procedure	≈	Drug assumption: 👍* Kelner/SF-36/Backill: ≈	MRI: ≈	≈
	4w			≈	Drug assumption/Backill: 👍* Kelner/SF-36: ≈		
	6w			≈	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
	3m			↓*	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
	6m			↓*	Drug assumption/Kelner/SF-36: ≈ Backill: 👍*		
Paradiso, 2005	4-6m	Microdiscectomy	Ozone	NI	👎		NI
	1y			NI	👎	MRI/CT: 👎	
	3y			≈	👎	EMG: ≈	
Apuzzo, 2014	1m	Ozone	GPR	↓*		MRI: NC	NC
	1-5y			≈		MRI: NC Recurrence: 👍*	
	1m	Ozone + GPR	GPR	↓*		MRI: NC	
	1-5y			↓*		MRI: NC Recurrence: 👍*	

🡻 Reduction of pain in experimental versus control; 👍 Better outcome in experimental versus control; 👎 Worse outcome in experimental versus control; ≈ Similar outcome in experimental versus control; ≠ Differences on MRI results were found but only as a tool to predict response to treatment; *Statistically Significant Differences; w: weeks; m: months; y: years; NI: No Information; NC: No Comparison; VAS: Visual Analog Scale; SF-36: Short Form 36 Questionnaire; ODI: Oswestry Disability Index; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; EMG: Electromyogram; GPR: Global Postural Re-educatio

Figure 1. PRISMA flow diagram of article selection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary File

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3; 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4; Table I
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4; Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4; Table II
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5; Table I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table II and II
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5; Table II

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5; 6; 7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5; 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5; 6; 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12; 13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; NA: Not applicable

ANEXOS

ACTA REUMATOLÓGICA PORTUGUESA
SPR – Sociedade Portuguesa de Reumatologia

Normas de publicação

Objectivos e âmbito

A Acta Reumatológica Portuguesa (ARP) é uma publicação científica internacional, revista por pares, abrangendo aspectos clínicos e experimentais das doenças reumáticas. São publicados artigos originais, artigos de revisão, casos clínicos, imagens em Reumatologia, cartas ao editor e artigos que visam melhorar a Prática Clínica (recomendações e protocolos clínicos, por exemplo).

A ARP foi fundada em 1973 como orgão científico oficial da Sociedade Portuguesa de Reumatologia e subscreve os requisitos para apresentação de artigos a revistas biomédicas elaboradas pela Comissão Internacional de Editores de Revistas Médicas (*International Commitee of Medical Journal Editors*), publicada na íntegra inicialmente em N Engl J Med 1991; 324: 42428 e actualizada em Outubro de 2008 e disponível em www.ICMJE.org. A política editorial da ARP segue as Recomendações de Política Editorial (*Editorial Policy Statements*) emitidas pelo Conselho de Editores Científicos, disponíveis em http://www.councilscienceeditors.org/files/public/entire_whitepaper.pdf.

A ARP publica preferencialmente artigos escritos na língua Inglesa. Caso os autores optem por submeter em Português, poderá ser solicitada a sua tradução para a língua Inglesa. O rigor e a exactidão dos conteúdos, assim como as opiniões expressas, são da exclusiva responsabilidade do(s) autor(es).

Os artigos submetidos devem ser originais e não podem ter sido publicados previamente.

Os artigos publicados constituirão propriedade da revista, não podendo ser reproduzidos, no seu todo ou em parte, sem a prévia autorização dos editores.

A Revista está indexada no PubMed/Medline e os seus artigos estão disponíveis online na íntegra, com acesso aberto e gratuito.

Instruções para submissão de artigos

A Acta Reumatológica Portuguesa oferece aos autores um sistema de submissão e revisão de artigos a funcionar exclusivamente *online*. Acedendo ao *website* da ARP (www.actareumatologica.pt) os autores poderão submeter os seus artigos e acompanhar o seu estado no processo de revisão. Os autores serão notificados por email no próprio dia em que o(s) seu(s) artigo(s) sofra(m) alterações relevantes durante o processo editorial.

De modo a submeter um manuscrito, os autores deverão **criar uma conta de utilizador**:

- Aceder ao *website* da ARP (www.actareumatologica.pt), clicar no *link* "Entrar", seguido de "Registo" e seguir cuidadosamente todas as instruções fornecidas. Um email de activação será enviado para a sua conta de email. Para activar a conta ARP é necessário seguir o *link* fornecido no corpo desse email, que automaticamente o redirecionará para uma mensagem de registo no *website* da ARP.

Após a criação de uma conta ARP, os autores poderão **submeter e acompanhar o progresso do(s) seu(s) artigo(s):**

- Aceder ao ***website*** da ARP (www.actareumatologica.pt), entrar na area privada e clicar no *link "Submeter artigo"*. Preencher o formulário seguindo as instruções cuidadosamente.

Instruções aos autores

Para evitar atrasos no processo de revisão, leia cuidadosamente as instruções e assegure-se de que o seu manuscrito está de acordo com os requisitos da ARP antes de submeter (número de palavras e formato).

- Título do artigo: o título deve descrever brevemente o conteúdo do artigo. Não devem ser usadas abreviaturas. Deve ser indicado um curto título para rodapé. Nos artigos escritos em português é necessário incluir o título em inglês.

-Nome dos autores e afiliações

- Informações do autor responsável pela correspondência: nome, morada, telefone e endereço electrónico

- Resumo: com um máximo de 350 palavras ,deve incluir objectivos, material e métodos, resultados e conclusões. Para os casos clínicos o limite de palavras é 180.

Tipos de artigo:

- **Editoriais:** Os Editoriais serão solicitados por convite do Editor e constituirão comentários sobre tópicos actuais ou sobre artigos publicados na revista. O texto dos Editoriais não deverá exceder as 1200 palavras, um máximo de 15 referências e pode conter uma figura ou tabela.
- **Artigos de Revisão:** Preferencialmente, os Artigos de Revisão serão também solicitados pelo Editor. No entanto, os autores interessados em apresentar um Artigo de Revisão podem contactar o Editor para discussão dos temas a apresentar no artigo, o qual não deverá exceder as 4000 palavras, 6 Tabelas ou Figuras e 100 referências;
- **Artigos Originais:** O texto dos Artigos Originais deve ser apresentado com uma Introdução, Material e Métodos, Resultados, Discussão e Conclusão. Não deverá exceder as 4000 palavras, 6 Tabelas ou Figuras e 60 referências;
- **Prática Clínica:** O texto dos artigos de Prática Clínica deve ser apresentado com uma Introdução, Material e Métodos, Resultados, Discussão e Conclusão. Não deverá exceder as 4000 palavras, 6 Tabelas ou Figuras e 60 referências;
- **Casos Clínicos:** O texto dos Casos Clínicos deverá ser apresentado com uma Introdução, Caso Clínico e Discussão. Os Casos Clínicos deverão ser acompanhados de figuras ilustrativas/tabelas (máximo de 6), não deverão exceder as 2000 palavras e 25 referências;

- **Imagens em Reumatologia:** Imagens representando manifestações clínicas raras ou de particular interesse podem ser submetidas (no máximo 4). O texto acompanhante não deverá exceder as 500 palavras e 5 referências
- **Cartas ao Editor:** As Cartas ao Editor deverão constituir um comentário critico a um artigo da Revista ou uma pequena nota sobre um tema ou caso clinico. O texto não deverá exceder as 600 palavras, uma Figura/Tabela e um máximo de 10 referências.

Tabelas: As Tabelas a inserir devem ser assinaladas no texto em numeração romana. Cada Tabela deverá possuir um título e não deverá apresentar linhas verticais. As linhas horizontais só deverão ser usadas como separadores de título e subtítulos. Todas as abreviaturas usadas devem ser explicadas na parte inferior da Tabela.

Figuras: As Figuras a inserir devem ser assinaladas no texto em numeração árabe e apresentar legendas. Cada Figura deve ser importada individualmente em format JPEG ou TIFF de alta qualidade. O Editor reserva o direito de agrupar Figuras ou alterar o seu tamanho de modo a rentabilizar o uso da páginas.

Referências: As Referências bibliográficas devem ser classificadas e numeradas por ordem de entrada no texto e em *superscript*. As abreviaturas usadas na nomeação das revistas devem ser as utilizadas pelo *Index Medicus*. Nas Referências com 6 ou menos autores, todos devem ser nomeados. Nas Referências com 7 ou mais autores, devem ser nomeados os 3 primeiros seguidos de et al. Os números de página inicial e final devem ser totalmente apresentados (ex. 565-569 e não 565-9). Não indicar o número da Revista nem o mês da publicação. As Referências correspondentes a trabalhos não publicados, apresentações ou observações pessoais, devem ser inseridas no próprio texto (em parenthesis) e não como Referências convencionais. Os autores são responsáveis pela exactidão das Referências apresentadas.

Seguem-se alguns exemplos de como devem constar os vários tipos de Referências:

Revista
Nome(s) e iniciais do(s) autor(es). Título do artigo. Nome da Revista Ano; Volume: Página (s).
Ex: Hill J, Bird HA, Hopkins R, Lawton C, Wright C. Survey of satisfaction with care in a rheumatology outpatient clinic. Ann Rheum Dis 1992; 51: 195-197.

Artigo publicado *online* (inserir DOI)
Nome(s) e iniciais do(s) autor(es). Título do artigo. Nome da Revista Published Online First: data. doi.
Ex: Merkel PA, Curthbertson D, Hellmich B et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008.097758.

Capítulo de livro

Nome(s) e iniciais do(s) autor(es) do capítulo. Título do capítulo. In: Nome(s) e iniciais do(s) editor(es) medico(s). Título do livro. Cidade: Nome da casa editorial, ano de publicação: primeira a última página do capítulo.

Ex: Stewart AF. Hypercalcemia resulting from medications. In: Favus MD, ed Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. New York: Raven Press, 1991: 177-178.

Livro

Nome(s) e iniciais do(s) autor(es). Título do livro. Cidade: Nome da casa editorial, ano de publicação: página(s).

Ex: Lorig K. Patient Education. A practical approach. St Louis: Mosby-Year Book, 1992: 51.

Documento electrónico

Título do documento. http://address. Data de acesso.

Ex: Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde – Divisão de Doenças Transmissíveis, Março de 2005. http://www.dgsaude.pt/upload/membro.id/ficheiros/i006875.pdf. Accessed in January 25th 2008.

Agradecimentos

Incluir nesta secção agradecimentos a pessoas que tenham contribuído para o trabalho mas sem autoria. Instituições ou fontes de apoio financeiro também poderão aqui ser indicadas.

Processo de Revisão

Os artigos submetidos são enviados a revisores especializados no tema do artigo. Concluída a revisão do artigo, os autores são notificados, recebendo os pareceres e comentários dos revisores acerca do estado do mesmo. Com base nesses pareceres, os autores deverão editar o artigo, corrigi-lo e resubmetê-lo para nova revisão. Na resubmissão de um artigo terão de ser incluídas em anexo uma carta-resposta aos Revisores e um .doc com uma versão do artigo em *track changes*. Este documento não deverá ter qualquer identificação dos autores nem as respectivas afiliações. Caso o artigo se mantenha sem uma resposta dos autores durante mais de 6 meses, a Equipa editorial reserva-se no direito de o retirar do processo de revisão.

Critérios de Revisão

Os critérios de aceitação de um artigo para publicação têm em consideração a qualidade e originalidade do artigo apresentado, a excelência na redacção e organização do mesmo e o potencial impacto na literatura médica.

Todos os artigos aceites para publicação serão mantidos e apresentados como "*online-first*" até que os Editores os seleccionem para integrar um número específico da Revista.

Revisão de provas

Os autores dos artigos aceites para publicação receberão uma versão digital da prova do artigo para valiação. Assim, as provas devem ser revistas durante as 72h que sucedem a sua recepção. Os autores são responsáveis pela cuidada revisão do texto, Figuras, Tabelas, Legendas e Referências, e deverão contactar os Editores no caso em que sejam necessárias alterações. Apenas pequenas alterações e correcções tipográficas são permitidas nesta fase.

Direitos de autor

Após aceitação para publicação, os autores transferem para a ARP os direitos de autor do manuscrito.