Complementary Therapies in Medicine xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Critical appraisal of the systematic review and meta-analysis of intra-articular ozone therapy efficiency to attenuate pain in knee osteoarthritis

In the recently published systematic review from Noori-Zadeh et al.[1] in *Complementary Therapies in Medicine*, about the intra-articular ozone therapy efficacy and effectivity of intra-articular ozone therapy to reduce pain in knee osteoarthritic subjects, the authors suggest that the use of intra-articular injection of ozone gas may be an effective way to relieve disease-associated chronic pain. We decided to critically appraise their systematic review and meta-analysis and although the review focuses on an interesting research field, we would like to highlight some inaccuracies and flaws detected in the study that may uncertainty the conclusions of Noori-Zadeh and colleagues.

We have observed in the Noori-Zadeh et al.[1] manuscript that there is an extensive discrepancy between references shown in Table 1 with those listed in the *References* section of the manuscript. To give an example, Hashemi et al.[2] study appear as reference number 3 in Table 1 (Noori-Zadeh et al's.[1] manuscript) but in the *References* section the position, number 3, corresponds to the study of Booci et al.[3] study while Hashemi et al's.[2] is referenced in the 10th position. The issue related here extends to all the studies included in Table 1 from Noori-Zadeh's[1] study (see Table 1 from this manuscript).

There are major concerns that would lead to serious flaws related to the journals listed as references in Noori-Zadeh's[1] study. More specifically, we have observed that Hashemi M et al's study,[4] has been referenced in the Noori-Zadeh's[1] study as published in the *Journal Health Science*, but it was published in the *International Journal of Medical Research & Health Sciences*.[4] A similar circumstance affects Fernández-Cuadros et al.[5] study, which appears referenced in the manuscript as published in the journal *Biomarkers*, but it was published in the *Middle East magazine J Rehabil Health Stud (2018)*.[5]

In relation to the applied methodology, Noori-Zadeh et al.[1] defined as a specific inclusion criteria measures of pain obtained through VAS and WOMAC scales. However, there are four studies included where the authors did not offer WOMAC data (Feng et al.[6]; Calunga JL et al.[7]; Hashemi et al.[8]; Hashemi et al.[4]), and were included in Noori-Zadeh et al's.[1] study what suppose a non-compliance of the reported inclusion criteria. Additionally, Noori-Zadeh et al.[1] have not clearly indicated which variables, VAS or WOMAC, were used to develop the analysis in their study. It is intriguing how VAS or WOMAC scores were analyzed as WOMAC data was not provided in a number of studies.

Deep analysis of data shown by Noori-Zadeh et al.,[1] at their Table 1 shows several inconsistencies. Lopes de Jesús et al.[9] study reports VAS scale data collected in their original study published in *Plos One* which does not match those shown in Table 1 of the meta-analysis. VAS scale, originally reported, showed from the baseline until 8 weeks post-treatment, 7.2 (2.1) versus 7 (4.37), while Noori-Zadeh A et al.[1] study data shown at 8 weeks 1.7 (2.6) versus 0 (4.37).

Similarly, when we analyze Raeissadat et al. study,[10] we could observe that data corresponding to WOMAC included in Table 1 of Noori-Zadeh A et al's.[1] study, corresponds to total WOMAC and not WOMAC *pain*, being the latter (9.3 ± 4.4 (pre) and 3.2 ± 1.6 (post).[10]

Furthermore deep review of data provided by studies of Hashemi M et al., 2016[4] and 2017,[3] found that in the study from 2016[4] data corresponding to VAS scale (9 ± 1.43 vs. 3.38 ± 1.79) does not match with those included in meta-analysis (9 (1.43) (pre) 1.43 (post)). In this study, there is no data from WOMAC. Also in Hashemi et al's study from 2017,[8] post-intervention results corresponding to the VAS scale (2.2 (1.5)) are not provided in the original paper, but appear in a figure, from which is not possible to extrapolate the data, but we acknowledge that the authors could have asked Hasemi and colleagues for the raw data.

In the Colunga and colleagues study[7] it is reported that at the beginning of the sessions the average was 9 on the VAS scale and that at the end of the treatment it was 1. The standard deviation that appears in Noori-Zadeh A et al's study,[1] 0.02, which is not reported in the original article.

We found more inconsistencies when analyzed Mutlu et al.'s[11] study, included in Noori-Zadeh et al.'s[1] meta-analysis, when we observed the value to VAS scale at the beginning of treatment appear a value of 3.5 (± 1.5) in Noori-Zadeh et al.'s[1] manuscript but in Table 1 from Mutlu et al.'s[11] manuscript appear a value of 7.2 (± 1.1) 1.1) to VAS scale. Regarding WOMAC scale in the meta-analysis, it is reported that initially, the group had a score of 31.1 (12.9) which does not match any of the values shown in the Mutlu et al[11] study nor for total WOMAC 76.0 ± 11.9 or even WOMAC *pain* 16.0 ± 2.7. The data related to total baseline WOMAC, showed in the Noori-Zadeh et al.'s[1] meta-analysis, appear 31.1 (12.9), but this data corresponds to the total WOMAC data after one month of treatment according to Table 2 from Mutlu et al.'s[11] manuscript, not to the total baseline WOMAC. In this case, there has been a totally wrong transposition from the original paper data to the meta-analysis.

After carefully review of Fernandez-Cuadros et al.[5] study, we found that Noori-Zadeh A et al.[1] have included data from WOMAC *pain* and not from total WOMAC, so they use no comparable variables to develop their meta-analysis. Data extraction regarding the outcome of interest is a vital part of meta-analysis. Elements determining inclusion in the analysis are study design, population characteristics, type of treatment or exposure, and finally outcome measures (Berman & Parker).[12] We do not describe here a situation derived from pooling data with different metrics (but obtained from the same outcome) in this circumstance the measure of total WOMAC provides data that is not comparable to measures obtained from WOMAN pain.

Deep analysis of the data provided in the manuscript from Babaei-Ghazani A et al's[13], showed that authors used a VAS pain scale from 0 to 100 points. We have observed that Noori-Zadeh A et al's[1] study arbitrary divided by 10 the scale, so from an original value of 7735 in VAS pain scale in Babaei-Ghazani A et al's[13] study, a score of 7.735 is reported in the meta-analysis. Similarly, at the end of treatment in the Babaei-Ghazani A et al's study a score of 53.16 (26.771) is reported but

https://doi.org/10.1016/j.ctim.2019.102244
Received 12 November 2019

Table 1
Bibliographic inconsistencies found in the Noori-Zadeh A et al, 2019 manuscript.[1].

Article Title	Study	Journal References	Comments to journal	Reference number (table 1) in original manuscript	Reference order in original manuscript
Comparison between Intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study.	Carlos César Lopes de Jesus, 2017	PLoS One. 2017 Jul 24;12(7):e0179185.	None	1	8
Intra-articular ozone or hyaluronic acid injection: Which one is superior in patients with knee osteoarthritis? A 6-month randomized clinical trial	Seyed Ahmad Raeissadat, 2018	J Pain Res. 2018;11:111-117	None	2	9
The Effects of Prolotherapy With Hypertonic Dextrose Versus Prolozone (Intraarticular Ozone) in Patients With Knee Osteoarthritis	Masoud Hashemi, 2015	Anesth Pain Med. 2015 ;5(5):e27585.	None	3	10
Therapeutic Efficacy of Ozone Injection in to the Knee for the Osteoarthritis Patient along with Oral Celecoxiband Glucosamin	Xu Feng, 2017	J Clin Diagn Res. 2017;11(9):UC01-UC03.	None	4	15
Application of OzoneTherapy in Patients with Knee Osteoarthritis	José Luis Calunga, 2012	Ozone Sci Eng. 2012;34(6) 469-475.	Ozone: Science & Engineering	5	11
Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options	Tahir Mutlu Duymus, 2017	Knee Surg Sports Traumatol Arthrosc. 2017;25(2):485-492.	None	6	12
Effect of intraarticular injection of ozone on inflammatory cytokines in knee osteoarthritis	Masoud Hashemi, 2017	J. Cell Mol Anesth. 2017;2(2):37-42	None	7	13
The Comparison between Two Methods for the Relief of Knee Osteoarthritis Pain: Radio frequency and Intra-Periarticular Ozone Injection: A Clinical Trial Study	Masoud Hashemi, 2016	Health Sci. 2016;5(7S):539-546.	*Published in: International Journal of Medical Research & Health Sciences, 2016, 5, 7S:539-546*	8	14
The effects of ultrasound guided corticosteroid injection compared to oxygen–ozone (O2–O3) injection in patients with knee osteoarthritis: a randomized controlled trial	Arash Babaei-Ghazani, 2018	Clin Rheumatol. 2018	Clin Rheumatol. 2018 Sep;37(9):2517-2527	9	16
Intra Articular Ozone Reduces Serum Uric Acid and Improves Pain, Function and Quality of Life in Knee Osteoarthritis Patients: A Before - and - After Study.	Marcos Edgar Fernandez-Cuadros, 2018	Biomarkers. 2018;14(16):17.	Published in: Middle East J Rehabil Health Stud. 2018, 5(3); e68599.	10	17

in Noori-Zadeh A et al's[1] study reports a value of 5.316 ± 2.671. Furthermore and surprisingly we have found that such arbitrary division was applied to WOMAC scale too, we find in Babaei-Ghazani A et al's[13] study at the beginning of treatment reported a score of 65.24 (20.788) but in meta-analysis the value showed was of 6.261 ± 2.0871, and similarly to the end of the treatment with 49.71 (23.368) and 4.781 ± 2.0186 scores respectively.

Finally, we would like to summarise the major findings from the analysis of Noori-Zadeh et al's[1] study: i) The meta-analysis is irreproducible and has a serious problem of heterogeneity that may affect the interpretation of the results; ii) We have observed that several of the journals, from where the studies were included in this study, have uncertain scientific quality; iii) The data transposition from the original studies to the meta-analysis has major flaws; iv) Respecting the main

outcomes of the meta-analysis, VAS and WOMAC scales, we have observed that WOMAC was not analyzed in all cases, in some studies it is included in the analysis indistinctly from WOMAC or WOMAC pain; v) There are severe inaccuracies regarding bibliographic citations which is unacceptable in a systematic review (affecting both the in-text citing and the order in which they should appear in the References section of the manuscript)

We conclude from our analysis of the Noori-Zadeh and colleagues manuscript that the meta-analysis performed does not allow to derive any conclusion due to severe flaws in its development. Conclusions derived from the study do not provide valid scientific evidence, and actually it deserves at least to recompute the meta-analysis prior to include their conclusions in the body of knowledge.

Founding source

Research describe in this manuscript, has not received founding.

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