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Use of medical ozone in fail back surgery syndrome: a systematic review.

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ABSTRACT

The safety and efficacy of ozone injections in the spine for lumbar disc herniation has been proved in two systematic reviews with one metaanalysis. Many other papers with lower evidence level were published before encouraging its use for this pathology and other degenerative spinal diseases.
Fail back surgery syndrome (FBSS) is a terrible situation with no clear treatment option presently. Some authors have dared to use ozone injections in these patients, based on its antiinflammatory action and its highly save portfolio. Due to the great disability and dramatic situation of FBSS patients, a systematic review is mandatory in order to clarify the potential role of ozone in this pathology.

Key words
ozone therapy, fail back surgery syndrome, FBSS

1 Introduction.

Fail back surgery syndrome (FBSS) is defined as "spinal lower back pain of unknown origin that persists at the same site of the original pain despite surgical interventions, or appears after the procedure."[1]. Its incidence in patients undergoing back surgery ranges from 12[2] to 40[3] depending on the original surgical technique. The symptoms include persistent or recurring low back and/or leg pain. Possible organic causes of FBSS include[2]: epidural fibrosis; arachnoiditis; mechanical factors; inflammation-induced changes in the nerve roots; structural changes in the vertebral column; and lumbar degenerative disease. A myofascial pain syndrome (MPS), has been diagnosed in 85.7% of these patients[1].
Conservative treatments, such as medication and rehabilitation, usually produce unsatisfactory results[2]. Retrospective studies suggest that surgical revisions tend to have lower rates of improvement than the initial procedure[4]. Lysis of epidural adhesions as been referred to by some authors as a possible therapeutic option[1] but there is no consensus[5]. Treatment with spinal cord stimulation[6] and intrathecal drug delivery[7] produce good results and although their high costs, when compared with the costs related to hospital stay and re-operation or secondary surgeries, these procedures may worth their cost and provide better long-term results[8].
In the last three decades, the application of ozone has emerged as a potential therapeutic option for patients with FBSS. It is suggested that ozone is useful for treating low back pain (LBP) due to its analgesic and anti-inflammatory properties[9]. Although ozone therapy is not validated yet to treat FBSS it has proved to be safe and effective to treat lumbar disc herniation[10,11]; its cost is low and it is a minimally invasive procedure, which yields a new therapeutic option for the FBSS's patients
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2 Material and methods.

We have done an evidence review on the use of medical ozone in FBSS. Firstly,

we have done and advanced search in Web-of-Science - WOS, Pubmed and Embase databases by using the term's combination: 'ozone AND ("fail back surgery" OR FBSS OR (spine AND fibrosis) OR epidurolysis)' in the fields TITLE and ABSTRACT. After duplicates removal, we got 9 papers[12,13,14,15,16,17,18,19,20]. We read the abstract and rejected 2 papers [13,16] that were out of the scope of our target and a third one that was an editorial[19]. Secondly, we reviewed the references in the 6 remaining publications and were able to find one more paper[21] potentially useful. After a full reading of all the 7 papers, we dismissed two[15,21] because they did not study FBSS as a different entity inside the group of patients with chronic LBP, not showing detailed results for this problem. The quality level of the papers was evaluated according the Scottish Intercollegiate Guidelines Network (SIGN) that provides checklists[22] for different designs of studies (clinical trials, cohorts, case/control).

3 Results.

We compiled 2 prospective cohort studies without control group and 3 retrospective cohort studies without control group. The absence of randomized control trials makes impossible to perform a metaanalysis study.

3.1 Quality assessment.

The quality of the five papers was evaluated using the SIGN checklist for cohort studies (table 1).

All were suitable for review although no paper could be classified as "high quality" due to the lack of control group. The authors compared their results with the natural history of FBSS or with the published results of other treatments. Bias and limitations were better referred in the prospective studies.

The main problem was the different treatments used:

- epidurolysis + epidural ozone insufflation, used in 2 papers,
- caudal epidural ozone injection, used in 1 paper,
- intradiscal + intraforaminal ozone injection, used in 2 papers,
- paravertebral ozone injection, used in 1 paper and
- systemic indirect endovenous ozone therapy (SIEVOT), used in 1 paper.

Table 1

SIGN checklist	Author / year / country				
Internal validity	Barbosa 2016/Brazil	Magalhaes 2013/Brazil	Hernandez 2013/Mexico	Alexander 2011/Italy	Muto 2008/Italy
The study addresses an appropriate and clearly focused question.	YES	YES	YES	YES	YES
The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY
The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY
The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	NO	NO	NO	NO	NO
What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NOT APPLY	0%	0%	NOT APPLY	NOT APPLY
Comparison is made between full participants and those lost to follow up, by exposure status.	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY
The outcomes are clearly defined.	YES	YES	YES	YES	YES
The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY	NOT APPLY
Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	NO	YES	YES	YES	NO
The method of assessment of exposure is reliable.	YES	YES	YES	YES	YES
Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES	YES	YES	YES	YES
Exposure level or prognostic factor is assessed more than once.	YES	YES	YES	NOT APPLY	NOT APPLY
The main potential confounders are identified and taken into account in the design and analysis.	YES	YES	NO	YES	YES
Have confidence intervals been provided?	YES	YES	YES	NO	NO
Overall assesment of the study					
How well was the study done to minimise the risk of bias or confounding?*	0	+	+	0	0
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	YES	YES	YES	YES	YES
Are the results of this study directly applicable to the patient group targeted in this guideline?	YES	YES	YES	YES	YES

* Rate the overall methodological quality of the study, using the following as a guide: High quality (++): Majority of criteria met. Little or no risk of bias. Results unlikely to be changed by further research. Acceptable (+): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. Low quality (0): Either most criteria not met, or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.

3.2 Reported clinical results.

The Brazilian team from the School of Medicine of the Federal University of Sao Paulo published in 2013[17] a prospective pilot experience of epidurolysis followed immediately by ozone insufflation in the pathological areas of the spine with very positive results. However, the publication from 2016[14], that is retrospective did not show so much benefit. Interestingly, initial values in Visual Analogic Scale (VAS) and Owestry Dissability Index (ODI) were quite similar.

Hernandez's study showed no benefit of a single caudal epidural injection, through hiatus sacrus, together a paravertebral injection at both sides of the levels affected by the surgery, followed by 2 sessions of paravertebral procedure one per week.

Retrospective paper from Alexander and cols. described positive results using VAS and Roland Morris Disability Questionaire (RMDQ) in 72% of FBSS patients treated with paravertebral injections together systemic ozone (SIEVOT). Adding epidurolysis and intradiscal injection increased the good and excellent results up to 78%. Muto in 2008 obtained 60% of good results with an intradiscal and intraforaminal injection in the same procedure; one month later the patient was evaluated and in case of poor or null result, a second application was done.

The results are summarized in table 2.

Table 2

Author Year country	Patients	Desing	Quality	Intervention	Outcomes	Timing	Results	Adverse events
Barbosa 2016 Brazil	19 VAS 8.5 ODI 37.6 RMDQ 14.5	Retrospective	0	Epidurolysis + epidural ozone 20 mL @ 30 mg/mL 1 session	VAS ODI RMDQ NPSI	3 weeks	VAS improved 17% p<0,01 ODI and RMDQ no change	??
Magalhaes 2013 Brazil	13 VAS 8 ODI 45	Prospective	+	Epidurolysis + epidural ozone 20 mL @ 30 mg/mL 1 session	VAS ODI DN4	24 weeks	VAS improved 70% ODI improved 42% p<0,01 Better result for low back pain	1 headache 1 transient lower limbs paraesthesias
Hernandez 2013 Mexico	30 VAS 7.4 ODI 63.5	Prospective	+	Caudal epidural 20 mL @ 30 mg/mL + 2 x 20 mL @ 30 mg/mL paravertebral 1 session 2 more paravertebral sessions	VAS ODI	8 weeks	No change	1 headache 12 LBP after the injection???
Alexandre 2011 Italy	1027 VAS ?? RMDQ ??	Retrospective	0	Phase 1: Paravertebral 10 mL @ 15 mg/mL + SIEVOT 50 mL @ 30 mg/mL 12 sessions + Phase 2: Epidurolysis + intradiscal 3-20 @ 35 mg/mL 1 session	VAS RMDQ	??	Final results combined VAS and RMDQ. Phase 1: 72% good results. Phase 1 + 2: 78% good results	2 painful injections in phase 1
Muto 2008 Italy	200 McNab ??	Retrospective	0	Intradiscal 3 mL @ 35 mg/mL + intraforaminal 10 mL @ 35 mg/mL 1-2 sessions	Modified McNab	48 weeks	60% good-excellent results	NONE

4 Discussion.

The epidurolysis followed by ozone insufflation through the epiduroscopic catheter remains controversial after the Barbosa's paper. It is difficult to understand why the got such different results using the same technique with the same surgical team and taking into account that pre-interventional status of the patients were very similar. I encourage the authors to compare both populations in order to clarify this question.

The negative result of Hernandez's publication can be criticized from different point of views. The use of radiological contrast prior to the ozone injection can produce an interaction of both substances not studied previously that could even consume all the ozone injected. In FBSS, the frequent fibrosis can surely block the progression of the gas, avoiding it arriving at the damaged areas. On the other side, the ozone concentrations diminishes dramatically as it leaves the tip of the needle, so long epidural needles (120-140 mm) should theoretically be much more useful, as they could place useful ozone amounts where they are needed. This is the reason, we think, that intraforaminal (Muto) and epiduroscopic ways of administration produce much better results, as seen in papers from Brazil and Italy.

Interestingly, the use of extra-canal (paravertebral) and systemic (SIEVOT) ozone administration in the paper of Alexander's team yield a significant benefit in 72% of FBSS patients. This can be easily understood by the association of MPS and FBSS commented in the Introduction section of this paper. Peripheral and central sensitization is usually forgotten by doctors addressing this pathology and should be always checked (only Brazilian team used Neuropathic Pain Symptom Inventory (NPSI) and Douleur Neuropathique 4 (DN4)) and treated if present. This fact will, for sure, improve the results.

We must not forget to look for segmental instability that should be treated as best as possible, as many of these patients are reluctant to more open surgery.

5 Conclusions.

From the evidence found, ozone minimally interventional procedures are promising but we are far away to establish a recommendation. At least, prospective comparative studies should be done to whether recommend them or not.

The intradiscal + intraforaminal approach is simple with no side effects found in this revision and can be a good option until epiduroscopic approach clarifies its efficacy.

Phase 1 treatment in Alexander's study, also quite simple and secure, may be the first procedure to do if the patient does not want his spine "touched" again, a very common feeling.

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