International Journal of Dental Sciences and Research, 2016, Vol. 4, No. 2, 28-34
Available online at http://pubs.sciepub.com/ijdsr/4/2/4

DOI:10.12691/ijdsr-4-2-4

Efficacy of Ozone as an Adjunctive Anti-microbial in the Non-surgical Treatment of Chronic and Aggressive Periodontitis- Part 2: Review Findings and Meta-analysis

Oluwatosin Tokede[1,*], Yuri Jadotte[2], Abrar Tounsi[1]

[1]Dental Public Health, School of Public Health, Rutgers University
[2]Quantitative Methods, Epidemiology and Biostatistics, School of Public Health and School of Nursing, Rutgers University
*Corresponding author: tokedeom@sph.rutgers.edu

Abstract Chronic and aggressive periodontitis are known as inflammatory disorders which leads to tissue damage and bone loss. Ozone is a powerful oxidizer because of its ability to kill bacteria, fungi, inactivate viruses and it has been investigated as a potential anti-microbial in dentistry. The objectives were to compute a summary effect for the adjunctive use of ozone with scaling and root planning in the treatment of these diseases and to explore possible heterogeneity that may be present due to different ozone forms used during treatment. A detailed literature search was carried out across five databases and other sources to identify relevant studies. The effect size was the standardized mean difference (SMD) and 95% confidence interval calculated for clinical attachment level, probing depth, plaque index, bleeding on probing and gingival index. Between- study heterogeneity was assessed using the Q and I^2 tests. The results of the meta-analysis carried out on all outcomes are; CAL (SMD= -0.350, CI= -0.779, 0.078, p=0.109), PPD (SMD= -0.360, CI= -0.840, 0.119, p=0.141), PI (SMD= -0.496, -0.753 -0.239, p value=0.0002*) ,GI (SMD= -0.697, CI= -1.463, 0.070, p=0.075) and BOP (SMD= -0.143, CI= -0.504, 0.218, p= 0.438). The use of ozone with SRP improved all measures compared to SRP alone. The effects however, ranged from small to moderate and were statistically non-significant except for the PI scores. Sub-group analysis based on ozone form showed that use of ozone in oil significantly reduced the probing pocket depth (SMD= -1.09, CI= -1.617, -0.566) than ozone used in water or as gas. Ozone as an adjunct to SRP is painless and non -invasive and may still find application as a disinfectant in the non-surgical treatment of chronic and aggressive periodontitis. However, it only accounted for small to moderate non-significant clinical improvement of these diseases. This review highlights the need for additional high level evidence, i.e. well-designed experimental studies to provide insight on the optimal concentration of ozone, duration and frequency of application irrespective of the method of delivery before it can be considered part of routine treatment.

Keywords: *Chronic periodontitis, aggressive periodontitis, ozone therapy, scaling and root planning, clinical attachment level, probing pocket depth, plaque index, bleeding on probing, gingival index, adjunct, meta-analysis*

Cite This Article: Oluwatosin Tokede, Yuri Jadotte, and Abrar Tounsi, "Efficacy of Ozone as an Adjunctive Anti-microbial in the Non-surgical Treatment of Chronic and Aggressive Periodontitis- Part 2: Review Findings and Meta-analysis." *International Journal of Dental Sciences and Research*, vol. 4, no. 2 (2016): 28-34. doi: 10.12691/ijdsr-4-2-4.

1. Key Points

- Periodontal diseases are fairly common microbial infections which affect about one-third of the adult population worldwide [1]. It has been associated with several systemic conditions.
- Scaling and root planning (SRP) remain a major phase in the treatment of these diseases; however there are limitations associated with this procedure. There is, therefore a need to use adjunctive anti-microbials in addition to SRP to further reduce/eliminate micro-organisms count more specifically.
- Ozone therapy is quite inexpensive, predictable and conservative. The anti-microbial action is selective to microbial cells and does not damage human body cells.

2. Review Findings

Search results: The search of all included databases (appendix 1) and sources yielded 61 papers (Figure 1). Using Endnote, 22 duplicate papers were removed, 19 studies were further excluded based on information presented in the title and abstract that did not meet the inclusion criteria. Retrieved studies were included if they met the following criteria:

- were investigating the use of ozone
- had a randomized controlled parallel-arm or within participant (split mouth) design
- included subjects aged 18 years and older with a diagnosis of chronic and/or aggressive periodontitis

- Reported mean and standard deviation values of the primary outcome measures; clinical attachment level (CAL) and probing pocket depth (PPD) for the intervention and control groups.

The full text of 3 studies could not be retrieved for further examination, leaving only 17 studies that could be retrieved and assessed for eligibility.

6 studies were excluded as they did not meet the inclusion criteria. Eight studies were selected, but one study was in German and thus was excluded. Seven studies were subsequently included in the systematic review and meta-analysis based on the availability of data suitable for meta-analysis.

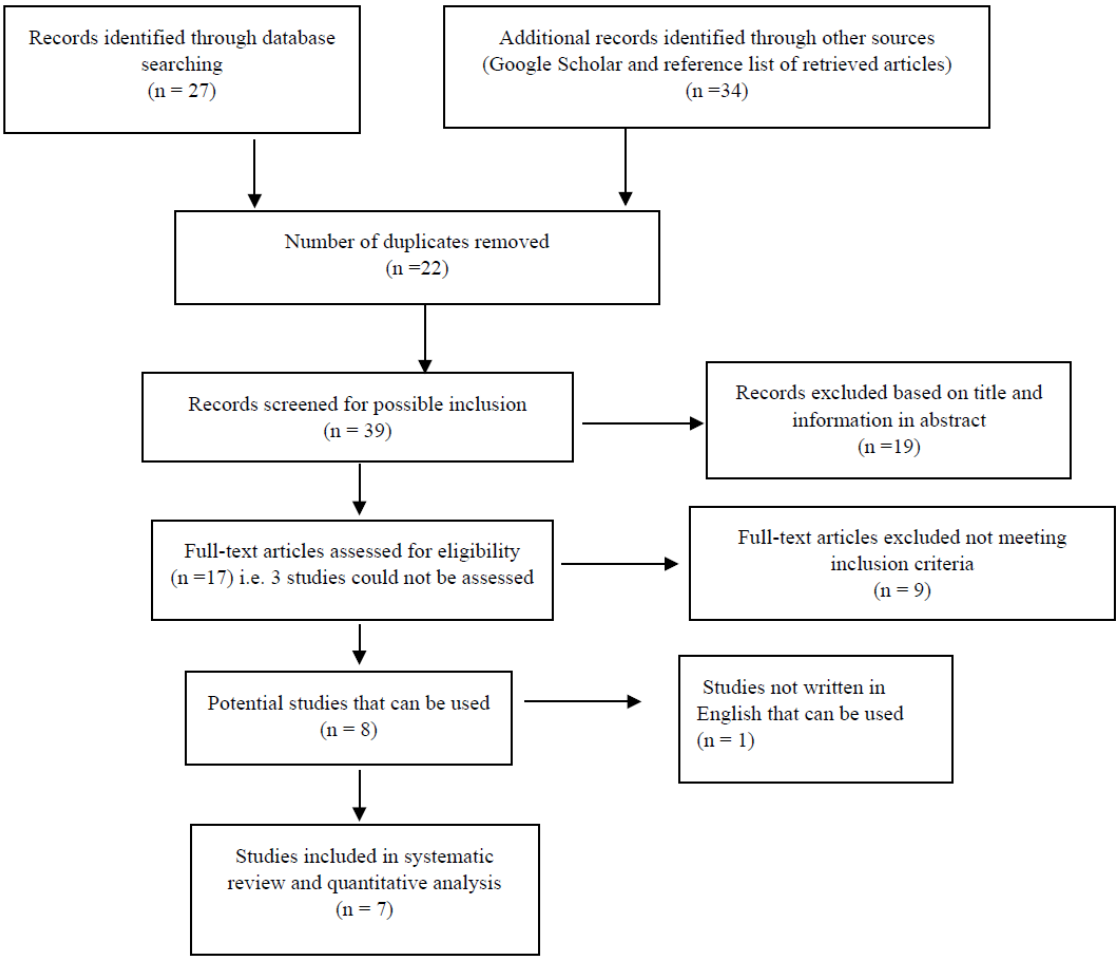


Figure 1. Schematic flow chart showing the results of study search and inclusion/exclusion criteria for review

Study characteristics: Seven studies were included in this review and meta-analysis [2-8]. Characteristics of included studies such as authors' names, age range of study participants, number of subjects, intervention, and control groups, duration, study design, clinical outcome measures reported and country where study was carried out are summarized in Table 1. Total number of subjects across all studies was 197 both males and females. The age distribution of participants in the included studies ranged from 20 – 72 years with a minimum required age of 18. Participants were healthy- no systemic conditions and non-smokers with disease severity ranging from moderate to severe based on the clinical attachment loss readings. All studies were conducted in a clinical setting. Study outcomes included any of these five clinical measures; plaque index (PI) score, gingival index (GI) score, bleeding on probing (BOP) score, probing pocket depth (PPD) and clinical attachment loss (CAL). All included studies reported PPD and CAL in millimeters which were the primary outcome measures of this review (Table 1).

Methodological assessment: Quality assessment was performed independently by two reviewers using the Revman Cochrane appraisal instrument [9] with criteria that include: randomization, concealment of treatment allocation, blinding of subjects and investigators, and use of intent to treat analysis. A decision rule of 4 low-risk scores was the basis for study inclusion. Five of the included studies were randomized parallel controlled clinical studies; the other two were randomized within-subject split-mouth design although method of randomization was not stated for one of the study [8]. The risk of selection bias from failure to conceal allocation was unclear in most studies [2,4,5,7,8]. Three studies [2,3,6] reported low risk of performance bias attributed to blinding of study investigators. One study [7] reported high risk of detection bias due to non-blinding of outcome assessor, four studies [2,3,4,5] reported low risk of detection bias while two [6,8] had unclear risk. For incomplete data assessment, two studies [2,5] reported high risk of attrition bias because subjects lost to follow-up were excluded from the analysis. All studies reported low risk of bias for selective outcome reporting- all outcomes were reported irrespective of its significance.

Data synthesis and statistical analysis: The sample size, mean differences and standard deviations were

entered for all studies so that the parallel-group studies and split-mouth studies formed two subgroups, which can be combined. A paired analysis was carried out by imputing within-patient correlations to account for the split-mouth design. The effect size used in this review is the standardized mean difference (SMD) between two treatment groups. Cohen's guidelines [10] for interpreting the magnitude of the SMD in the social sciences was used; small, SMD = 0.2; medium, SMD = 0.5; and large, SMD = 0.8. The standard difference in means with its standard error, variance, confidence intervals and p-value was calculated for all clinical outcome measures. A random effect model was used to account for variation in the true effect size between studies. Assessment of heterogeneity was done first by visual inspection of the meta-view/forest plot of each pooled outcome, using the value of I^2 test which indicates the magnitude of the heterogeneity and the Q test which indicates the statistical significance of this heterogeneity. Although the I^2 test and Q-test value reported low level of inconsistency between each outcome in the pooled analysis, the wide confidence intervals noted in each individual study on the forest plot indicates low precision in each study, which could have masked the presence of real heterogeneity.

Table 1. Characteristics of included studies for meta-analysis

Author	Age range (years)	Number of subjects	Intervention	Control	Duration	Design	Outcome	Location
Skurska et al 2010	25 - 68	34	Ozone gas + SRP	SRP	2 months	Randomized parallel design	PI BOP PPD* CAL	Poland
Hayakumo et al 2012	26 - 72	22	Ozonated water + SRP	SRP + water	2 months	Randomized controlled parallel design	BOP PPD CAL	Japan
Patel et al 2012	30 - 60	20	Ozonated olive oil + SRP	SRP	2 months	Randomized split mouth design	PI GI PPD CAL	India
Katti et al 2013	20 - 60	30	Ozonized water + SRP	SRP	1 month	Randomized split mouth design	PI GI PPD CAL*	India
Yilmaz et al 2013	37 - 67	20	Gaseous ozone + SRP	SRP	3 months	Randomized controlled parallel design	PI PPD CAL	Turkey
Shoukheba et al 2014	21 - 30	30	Ozonated oil + SRP	SRP	6 months	Randomized controlled parallel trial	PI GI BOP PPD CAL	Egypt
Al Habashneh et al 2015	23 - 65	41	Ozonated water + SRP	SRP	3 months	Randomized controlled parallel design	PI GI BOP PPD* CAL	Jordan

Figure 2 and Figure 3 shows the analysis of the primary outcome measures; CAL (SMD= -0.350, CI -0.779, 0.078, p=0.109) and PPD (SMD= -0.360, CI -0.840, 0.119, p=0.141). Since improvement is associated with lower scores on the outcome measures, patients who received ozone therapy in addition with SRP had a greater improvement in their measures than those who had SRP alone as indicated by the negative sign. However, this effects are small and statistically non-significant. Secondary outcome measures; PI, BOP and GI also reported improvement in the intervention group (figures 4-6). The PI scores reported statistical significance albeit a small effect (SMD=-0.496, CI=-0.753,-0.239, p=0.0002). The BOP (SMD=-0.143, CI=-0.504, 0.218, p=0.438) and GI scores were not statistically significant although patients in the intervention group reported a moderate improvement on the GI scores (SMD= -0.697, CI=-1.463, 0.070, p=0.075).

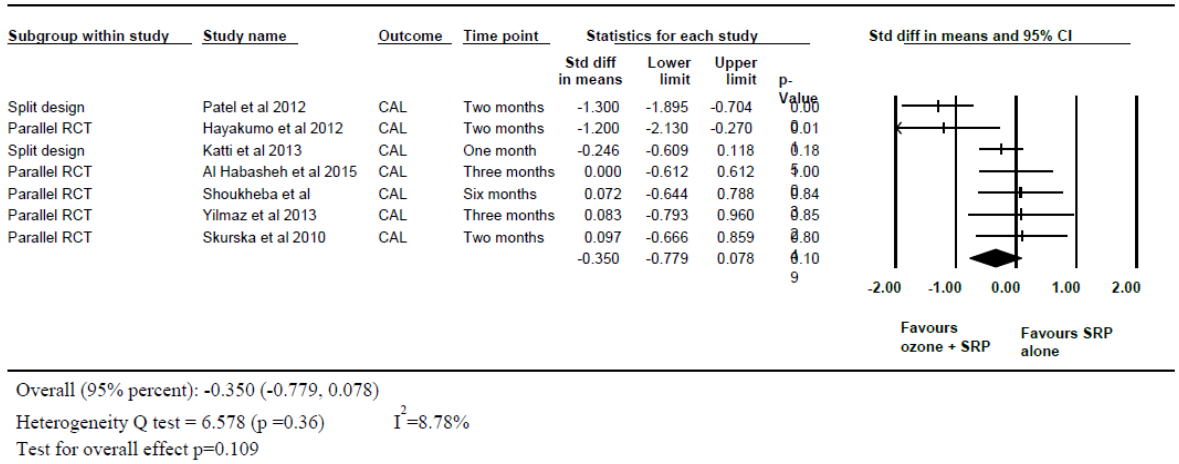
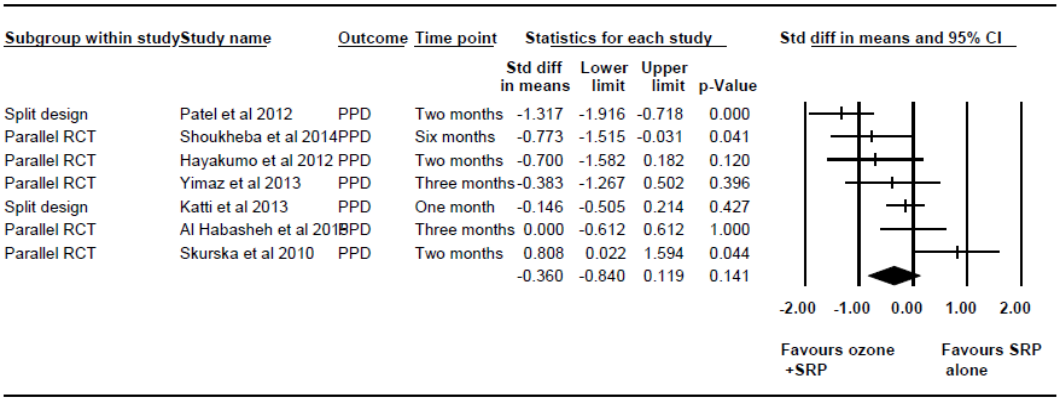
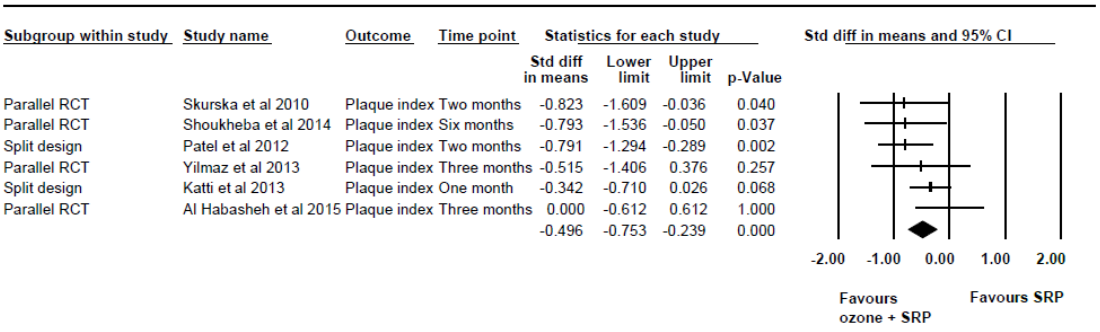


Figure 2. Meta-analysis of the effect of ozone on the CAL



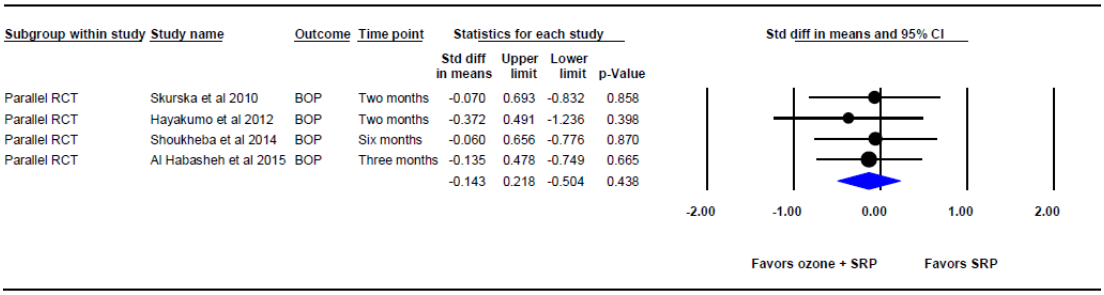
Overall (95% percent): -0.360 (-0.840, 0.119)
Heterogeneity Q-test =6.47(p=0.37) I^2=7.33%
Test for overall effect p=0.141

Figure 3. Meta-analysis of the effect of ozone on the PPD using a random effects model



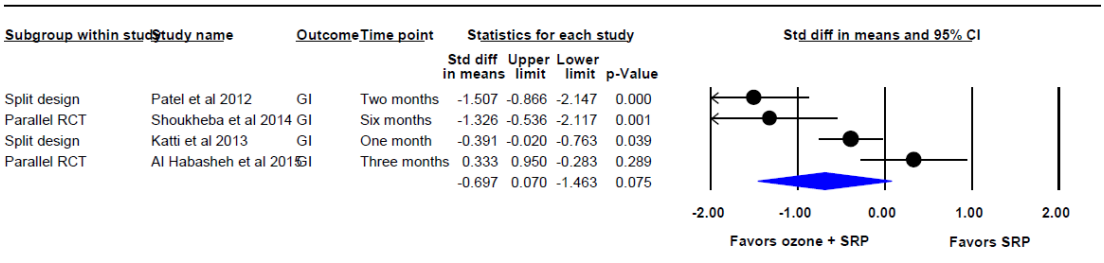
Overall (95% percent): -0.496 (-0.753, -0.239)
Heterogeneity Q-test=4.94 (p=0.4) I^2=0%
Test for overall effect p=0.0002*

Figure 4. Meta-analysis of the effect of ozone on the PI scores using a random effects model



Overall (95% percent): -0.143 (-0.504, 0.218)
Heterogeneity Q-test=0.359 (p=0.95) I^2=0%
Test for overall effect p=0.44

Figure 5. Meta-analysis of the effect of ozone on the BOP scores using a random effects model



Overall (95% percent): -0.697 (-1.463, 0.070)
Heterogeneity Q-test: 3.54 (p=0.315) I^2=0%
Test for overall effect p=0.075

Figure 6. Meta-analysis of the effect of ozone on the GI scores using a random effects model

Sub-group analysis by form of ozone used showed that ozone oil had a large mean effect on probing pocket depth reduction (SMD= -1.09, CI= -1.617, -0.566) which was significant (Figure 7). The use of ozone in oil seems more effective than ozonized/ozonated water and gaseous ozone (SMD= 0.1734 and 0.2307). Ozone oil was also found to have a moderate effect on the clinical attachment status.

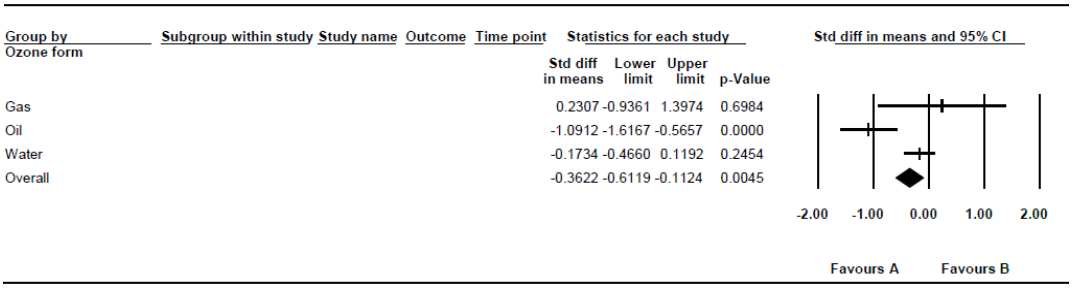


Figure 7. Forest plot showing effect of sub-group analysis by ozone form on PPD

Although not pre-specified in the protocol, sensitivity analysis was performed at different intra-patient correlation coefficient because these values were not recorded by the two split-mouth design studies included in this review. A value of 0.5 was assumed for the final analysis, since sensitivity analyses using correlation values of 0.25, 0.5 and 0.75 yielded similar results (Table 2).

Table 2. Sensitivity analysis at different intra-patient correlation coefficient values

Clinical measures	0.25				0.50				0.75			
	SMD	L.L	U.L	P value	SMD	L.L	U.L	P value	SMD	L.L	U.L	P value
CAL(mm)	-0.39	-0.83	0.05	0.085	-0.35	-0.78	0.05	0.11	-0.32	-0.69	0.05	0.09
PPD(mm)	-0.38	-0.88	0.12	0.136	-0.36	-0.84	0.12	0.14	-0.31	-0.74	0.11	0.15
PI*	-0.54	-0.83	-0.25	0.0002	-0.49	-0.75	-0.24	0.0002	-0.40	-0.63	-0.18	0.0003
BOP	-0.14	0.50	0.22	0.44	-0.14	-0.50	0.22	0.44	-0.14	0.50	0.28	0.44
GI	-0.78	-1.64	0.07	0.07	-0.69	-1.46	0.07	0.075	-0.62	-1.32	0.07	0.08

3. Discussion

The anti-microbial effect of ozone has been discussed extensively in the literature. Its mechanism of action results from oxidation of microbial components while protecting healthy cells from an uncontrolled activity of free radicals due to its content of superoxide dismutase, catalase, beta-carotene, methionine [8], etc. It is known that it brings about an anti-hypoxic effect in tissues [11]. This change in the sub-gingival environment suppresses the activity of anaerobic micro-organisms known to inhabit these periodontal pockets.

Although the pooled analyses for all outcomes were in favor of the intervention group, the magnitude of the treatment effect ranged from small to moderate using the Cohen's guideline. Summary effect size of the GI score indicates a moderate effect of -0.697 with no statistical significance while the summary effect size of the PI scores (-0.49) indicates a small effect with statistical significance. It is of note however to state that a non-significant p-value may not necessarily mean the absence of a clinically important effect as in the case of the GI score and vice versa. This review showed that treatment of chronic and aggressive periodontitis with adjunctive ozone did not provide superior benefits in terms of all reported clinical parameters when compared with SRP alone. The small to moderate treatment effect of this review finding may be explained partially by the different forms and concentrations of ozone used, duration of application and the limited number of available evidence.

This review included two different study designs; parallel and split mouth RCTs. Although, it did not matter whether the study design utilized a split mouth or a parallel design as the results were similar, it is important to comment on the shortcoming of the split mouth design. While it removes much of the inter-subject variability thereby increasing the power of the study compared to the parallel design, it is prone to the 'carry-across' effect of the intervention especially when it cannot be localized. Also, intra-patient correlation was not reported for the two split mouth studies. However, a modest value of 0.5 was chosen as sensitivity analysis performed at 0.25, 0.5 and 0.75 values respectively reported similar results. It is also argued that efficiency of this design is only noticeable when the correlation is high enough.

Interestingly, method of ozone delivery to periodontal tissues differed between studies; three [3,5,8] utilized ozonized/ozonated water, two [2,4] utilized gaseous ozone and the other two [6,7] utilized ozonized oil with varying concentration of ozone used. Further analysis based on method of delivery showed that ozone oil may prove more effective in reducing the probing pocket depth than ozone water or gas. This property of the former may be attributed to the long life span of ozone when dissolved in a viscous oil base, its long stay in the oral cavity, adequate penetration and a more localized effect on the tissue. Ozone in water is said to be highly unstable and rapidly decomposes at room temperature [8]. Also, the mean effect of ozone was not different across studies with regards to the clinical attachment level.

Some trials included in this review were judged to be of low quality that may be due to the lack of adequate blinding of subjects and clinical examiners. In addition, one has to consider the small number of included studies for this review, low power of included studies due to small sample sizes and the pooling of results from aggressive

and chronic periodontitis which may limit its generalizability. Also, difference in follow-up time may induce inconsistency across studies.

This review, however, has its strength; as with most meta-analyses, the pooling of information from individual studies provided a more precise estimate of the effect measure. Included studies were able to implement randomization using methods such as coin tossing and computer generated sequencing thereby minimizing bias due to selection. Concerning the clinical safety of ozone, no adverse events or side effects were reported in the included studies except for dentinal hypersensitivity that was reported in one study [6].

4. Conclusion

Ozone as an adjunct is painless and non-invasive and may still find application as an anti-septic in the non-surgical treatment of periodontal diseases. However, only small to moderate non-significant clinical improvement of these diseases was found for its adjunctive use in this review; more well-designed studies will be needed to provide insight on the optimal concentration of ozone, duration and frequency of application irrespective of the method of delivery before it can be considered a routine treatment.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

We thank Dr. Anna Skurska for providing additional information on her study upon request by us.

References

[1] Dusane, J., Mogal, V., Borse, P., Thakare, P., Kshirsagar, S. (2016). Recent trends in treatment of periodontitis. Pharmaceutical And Biological Evaluations;3(1): 19-31.

[2] Skurska A, Pietruska MD, Paniczko-Drężek A, Dolińska E, Zelazowska-Rutkowska B, Zak J, Pietruski J, Milewski R, Wysocka J (2010). Evaluation of the influence of ozonotherapy on the clinical parameters and MMP levels in patients with chronic and aggressive periodontitis; 55(2): 297-307.

[3] Hayakumo, S., Arakawa, S., Mano, Y. and Izumi, Y. (2013). Clinical and microbiological effects of ozone nanobubble water irrigation as an adjunct to mechanical subgingival debridement in periodontitis patients in a randomized controlled trial. Clinical Oral Investigations; 17: 379-388.

[4] Yilmaz S, Algan S, Gursoy H, Noyan U, Kuru B. E, Kadir, T (2013). Evaluation of the clinical and antimicrobial effects of the Er:YAG laser or topical gaseous ozone as adjuncts to initial periodontal therapy. Photomed Laser Surg; 31(6): 293-298.

[5] Al Habashneh R, Alsalman W, Khader Y (2015). Ozone as an adjunct to conventional nonsurgical therapy in chronic periodontitis: a randomized controlled clinical trial. J Periodont Res; 50: 37-43.

[6] Patel PV, Patel A, Kumar S, Holmes JC (2012). Effect of subgingival application of topical ozonated olive oil in the treatment of chronic periodontitis: a randomized, controlled, double blind, clinical and microbiological study. Minerva Stomatol; 61(9): 381-98.

[7] Shoukheba M.Y.M, Ali Sh. A (2014). The effects of subgingival application of ozonated olive oil gel in patient with localized aggressive periodontitis. A clinical and bacteriological study. Tanta Dental Journal; 11(1): 63-73.

[8] Katti, S. S., Chava, V. K. (2013). Effect of Ozonised water on Chronic Periodontitis - A Clinical Study. Journal of International Oral Health JIOH; 5(5): 79-84.

[9] Higgins JPT, Green S (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Available from www.cochrane-handbook.org.

[10] Faraone, S. V. (2008). Interpreting Estimates of Treatment Effects: Implications for Managed Care. Pharmacy and Therapeutics; 33(12): 700-711.

[11] Mani A, Shukla P, Patel R, Bhople T (2014). Ozone therapy in Periodontics- A review. Journal of Medical Science and Clinical Research. JMSCR; 2(12): 3352-3358.

Appendix 1: Search strategies across databases

Ovid MEDLINE **Last saved:6/7/2015**	**CINAHL** **Last saved :6/9/2015**	**COCHRANE** **Last saved: 6/9/2015**	**SCOPUS** **Last saved: 6/12/2015**	**ISI web of science** **Last saved: 6/27/2015**
1. Periodontitis/ or Chronic Periodontitis/ or Adult/ 2. (Clinical attachment loss or alveolar bone loss or periodontal pocket depth).mp 3. Periodontal diseases.mp. or Periodontal Diseases/ 4. Chronic periodontitis.mp. or Aggressive Periodontitis/ 5. (Ozone or ozone therapy).mp. 6. (Ozone water or ozonated water).mp.] 7. Ozone/ or ozonized water.mp. 8. (Gaseous ozone or ozone gas).mp.] 9. (Aqueous ozone or ozone oil or ozonized oil).mp. 10. Conventional periodontal therapy.mp. 11. (Non-surgical periodontal treatment or dental scaling or root planing).mp. 12. (Adjunct periodontal therapy or initial non-surgical periodontal	S1.periodontitis OR chronic periodontitis OR adult S2. clinical attachment loss OR periodontal pocket depth OR periodontitis S3. periodontal diseases OR alveolar bone loss S4. aggressive periodontitis OR chronic periodontitis S5. ozone OR ozone therapy OR ozonotherapy S6. ozonized water OR ozone water OR ozonated water S7. gaseous ozone OR ozone gas S8. aqueous ozone OR ozone oil OR ozonated oil S9. conventional periodontal therapy AND scaling AND root planning S10. non-surgical periodontal therapy AND scaling AND root planing S11. non-surgical periodontal therapy OR scaling OR root planing S12. adjunct non-surgical periodontal therapy OR scaling OR root planing OR	#1 adult periodontitis or chronic periodontitis #2 clinical attachment loss or probing pocket depth or periodontitis #3 periodontal diseases or alveolar bone loss #4 aggressive periodontitis or chronic periodontitis #5 ozone or ozone therapy or ozonotherapy #6 ozone water or ozonated water or ozonized water #7 aqueous ozone or ozone oil or ozonated water #8 gaseous ozone or ozone gas #9 conventional periodontal therapy or scaling or root planing #10 adjunct non-surgical periodontal therapy or scaling or root planing or	1.(periodontitis) OR (chronic periodontitis) OR (adult periodontitis) 2.(clinical attachment loss) OR (alveolar bone loss) OR (periodontal pocket depth) OR (chronic periodontitis) 3.(periodontal diseases) OR (alveolar bone loss) OR (clinical attachment loss) OR (chronic periodontitis) 4.(ozone) OR (ozone therapy) OR (ozonotherapy) 5.(ozone water) OR (ozonated water) OR (ozonized water) OR (aqueous ozone) 6.(ozone gas) OR (gaseous ozone) 7.(ozone oil) OR (ozonated oil) OR (ozonized olive oil) 8.(conventional periodontal therapy) OR (scaling) OR (root planing) 9.(non-surgical periodontal therapy) OR (dental scaling) OR (root planing)	1. Periodontitis/ or Chronic Periodontitis/ or Adult/ 2. (Clinical attachment loss or alveolar bone loss or periodontal pocket depth) 3. Periodontal diseases.mp. or Periodontal Diseases/ 4. Aggressive periodontitis.mp. or chronic Periodontitis/ 5. (Ozone or ozone therapy).mp. 6. (Ozone water or ozonated water).mp.] 7. Ozone/ or ozonized water.mp. 8. (Gaseous ozone or ozone gas).mp.] 9. (Aqueous ozone or ozone oil or ozonized oil).mp. 10. Conventional periodontal therapy.mp. 11. (Non-surgical periodontal treatment or dental scaling or root

therapy).mp. 13. (tooth mortality due to periodontitis or tooth loss due to periodontitis).mp. 14. (tooth mortality or tooth loss or clinical attachment loss or alveolar bone loss).mp. 15. 1 or 2 or 3 or 4 16. 5 or 6 or 7 or 8 or 9 17. 10 or 11 or 12 18. 13 or 14 19. 15 and 16 and 17 and 18	initial periodontal treatment S13. tooth loss due to periodontitis OR tooth mortality due to periodontitis S14. tooth loss due to periodontitis OR tooth mortality due to periodontitis OR clinical attachment loss S15. tooth loss due to periodontitis OR alveolar bone loss OR clinical attachment loss OR tooth mobility S16. S1 OR S2 OR S3 OR S4 S17. S5 OR S6 OR S7 OR S8 S18. S9 OR S10 OR S11 OR S12 S19. S13 OR S14 OR S15 S20. S16 AND S17 AND S18	initial periodontal treatment #11 tooth loss due to periodontitis or tooth mortality due to periodontitis #12 tooth loss due to periodontitis or tooth mortality due to periodontitis or clinical attachment loss #13 tooth loss due to periodontitis or alveolar bone loss or clinical attachment loss or tooth mobility #14 #1 or #2 or #3 or #4 #15 #5 or #6 or #7 or #8 #16 #9 or #10 #17 #11 or #12 or #13 #18 #14 and #15 and #16 and #17	10.(adjunct periodontal therapy) OR (dental scaling) OR (root planing) 11.(initial periodontal therapy) OR (dental scaling) OR (root planing) 12.(tooth loss due to periodontitis) OR (tooth mortality due to periodontal disease) 13.(tooth loss due to periodontitis) OR (clinical attachment loss) OR (alveolar bone loss) OR (tooth mobility) 14. #1 OR #2 OR #3 15. #4 OR #5 OR #6 OR #7 16. #8 OR #9 OR #10 OR #11 17. #12 OR #13 18. #14 AND #15 AND #16 AND #17	planing).mp. 12. (Adjunct periodontal therapy or initial non-surgical periodontal therapy).mp. 13. (tooth mortality due to periodontitis or tooth loss due to periodontitis).mp. 14. (tooth mortality or tooth loss or clinical attachment loss or alveolar bone loss).mp. 15. 1 or 2 or 3 or 4 16. 5 or 6 or 7 or 8 or 9 17. 10 or 11 or 12 18. 13 or 14 19. 15 and 16 and 17 and 18