Dental ozone therapy, the state of the art.

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ISCO3 documents are recommendations which may become source of guiding and reference to all those who practice ozone therapy. However, it is up to each ozone therapy to follow or not the recommendations issued by ISCO3.

Abstract

There has been very little research to support clinical practices in dental ozone therapies. The protocols used in dental ozone therapy should fulfill the general guidelines and requirements commonly recognized by healthcare professionals and authorities as evidence-based medicine. To meet these criteria, both ozone dental research and the clinical practice of dentistry should converge. The positive results and advantages of dental ozone therapy should define standard parameters that the dental ozone equipment manufacturers need to follow to develop ozone systems that meet the requirements of both dentists and researchers.

The aim of this paper is to review the available published research and to compare it to what the majority of practicing dentists are applying in their practice. Four databases (PubMed; Ovid Medline; Cochrane; ISCO3) were used to search for articles covering the use of ozone in dentistry. Using the key words "ozone in dentistry" on PubMed (last accessed November 2017) retrieved 295 articles. Articles not related to dental ozone and general reviews were excluded (70). The resulting sample size of 225 articles, ~~a~~s well as the retrieved analysis results, are highly indicative to be able to draw conclusions and to formulate future recommendations.

To our knowledge, this is the first attempt to perform such an analysis. It is not the aim of this paper to critique the published research or the clinical practice of dental ozone therapy. The aim is to elicit the required modifications to research protocols and to evaluate whether dental ozone manufacturers provide the required equipment.
This review study used different groupings to evaluate the results. In the "ozone gas only group", a clear deviation between research and clinical practice was noted. In all the other groups, the results were, in general, more congruent. Most of the current dental ozone research has focused on the antimicrobial effects of ozone, using either just ozone gas only, ozonated water only or ozonated oils only. It is highly recommended that dental ozone research changes its path. Clinicians have expectations that research will support their clinical uses of ozone. We need to meet the expectations of clinicians through adopting new and different studies. We need to create research that goes past the conventional and well-studied antimicrobial potential of ozone and by using ozone both in gas and water, not separately, plus ozonated oils when applicable.

Key words: Dental, ozone therapy, research, clinical expertise, ozone gas, ozonated water, ozonated oils.

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1. Introduction

Since the early pioneering days of the Swiss dentist Dr. E Fisch (1899-1966), ozone application in dentistry has evolved and now is being used by a growing number of dentists worldwide.

Due to the high disinfection and oxidation properties of ozone, scientists studied the use of ozone in various applications, mainly in water treatment, where the bulk of the fundamental ozone science as we know it today emerged. The promising results from the use of ozone in water treatment encouraged the expansion of its use to other applications, e.g. air and surface treatments, which are more relevant to healthcare and medical professionals.

In parallel to the use of ozone in industry in the early twentieth century, scientists and physicians also introduced the use of ozone in medical and dental applications. It was not until the last two decades of the 20th century that researchers studied the biological effects of ozone more in depth. Then, the clinical guidelines became more relevant and precise. This better understanding of ozone reactions and its biological effects led clinicians and researchers to re-study its use in dental medicine as well.

During this period, several national and international medical ozone associations were formed, the International Scientific Committee of Ozone therapy (ISCO3) was established, and a multitude of scientific congresses and courses were held. Ozone therapy is now legally practiced in several countries around the world. ISCO3 published the “Madrid Declaration on Ozone Therapy”[1] which is considered an international reference for both clinicians and legal authorities.

Even though there has been a steady increase of healthcare professionals using ozone, ozone therapy has not yet reached the point where it is considered a mainstream treatment modality. Consequently, it is not reimbursed by social security programs or by private insurance companies. Two large issues that pose major obstacles to ozone therapy advancement are the shortage of public research funds and the reticence of pharmaceutical companies to invest in non-patentable modalities. However, some of the many indications of ozone therapy are now classified as evidence-based medicine. Some high quality published clinical trials, meta-analyses, and the gathered clinical experience have proved ozone’s efficacy in certain medical applications.[1-5]

With the collaborative contribution and coordination of both research and clinical practice, the well-studied medical indications of ozone have reached the level of evidence-based science. Very clear guidelines and protocols were established and are constantly updated with new scientifically supported findings.

Dental ozone therapy constitutes the number one topical administration in medicine. Research and clinical applications in medical ozone therapy can be a reference to follow for dental research and its applications.

Even though there are published general reviews of available literature with conflicting findings and recommendations, there is a need to examine whether dentists are following the research methodology and if the protocols used are similar. There is also a need to evaluate the technical specifications of commercially available dental ozone systems. Such comparative analyses have not been carried out yet. We believe that the findings of these analyses will aid in highlighting any potential deviation that may exist between research and clinical practice and help direct future research. It is not within the objectives of this paper to evaluate or critique published literature, nor to assess the suitability of the protocols used by practicing dentists. The goals are both to reach a synergistic and common path in dental ozone therapy leading to evidence-based medicine as well as to provide standard requirements for the manufacture of ozone generators to meet the needs of dental practice. This would set more definitive guidelines to apply in general dental practices.

2. Methodology

2.1 Dental ozone published articles: Data collection

Four databases (PubMed; Ovid Medline; Cochrane; ISCO3) were used to search for articles covering the use of ozone in dentistry. Using the key words "ozone in dentistry" on PubMed (last accessed November 2017) retrieved 295 articles, some of which were not related to dental ozone uses. In addition, selected unpublished articles collected over the years from scientific ozone meetings were also used in this study. In total, 225 articles were included. This sample size of 225 articles, as well as the retrieved analysis results, are highly indicative to be able to develop conclusions and future recommendations as needed.

All 225 articles were used in this comparative analysis, irrespective of ozone form (gas, ozonated water or ozonated oil) or fields of application (*in vitro*, *pre-clinical* and clinical studies) were all included. Whenever possible, full text articles were retrieved. Otherwise abstracts were used – Included in Table 1.

As mentioned earlier, the aim is not to critique the studies, but to look at the "Materials and Methods" and the applied ozone parameters and compare them to those applied by the dentists in their practice. Percent of results (**G/S** Good/Significant, **G/NS** Good/non-significant, **NS** non-significant) was stabilized as criterion of clinical efficiency.

Table 1. Frequency distribution of articles by group classification *pre-clinical*- in *vitro*-clinical.

Group	**Number of Articles**	Type of article		Stage of the investigation		
		Abstracts	Full Text	*In vitro*	Pre-clinical	*Clinical trials*
I. O_3 Gas	118	59	59	72	39	7
II. O_3 Water	53	10	43	39	11	3
III. O_3 Oil	30	8	22	10	15	5
IV. O_3 Gas-Water	14	3	11	9	4	1
V. O_3 Topical-Systemic	6	2	4	-	3	3
VI. O_3 Injection	4	-	4	-	3	1
TOTAL	**225**	**82**	**143**	**130**	**20**	**75**

Sidebar I. Classification of articles

Group	Ozone mode of application
I. Ozone Gas	Ozone gas only was used in the research
II. Ozonated Water	Ozonated water only was used in the research
III. Ozonated Oil	Ozonated oil only was used in the research
IV. Ozone Gas-Water	Combined or Separate administration of ozone gas and ozonated water were used, plus ozonated oil when applicable
V. Ozone Topical-Systemic	Topical and/or Systemic ozone administration was used
VI. Ozone Injection	Ozone gas and/or ozonated water was injected sub-cutaneous or intra-articular

Classification of articles – Appendix: Reviewed Articles List. Articles were classified into six groups as listed in sidebar I.

2.2 Retrieved Data

Articles from each classification group were categorized according to different criteria: 1) country and period of research (Table 2), 2) field of research i.e. caries, periodontics, endodontic, soft tissue lesions, etc. (Table 3), 3) Ozone equipment/generator and technical specifications (Table 4).

Table 2. Classification of manuscript according to: County and period of research.

Country	1985 2004	2005 2010	2011 2015	2016 2017	**N**
Turkey	-	4	28	13	45
U.K.	20	4	3	1	28
Germany	7	6	3	3	19
Egypt	1	3	9	4	17
Brazil	-	3	9	4	16
Italy	2	7	3	2	14
India	-	1	9	4	14
Japan	7	5	2	-	14
Switzerland	1	6	2	-	9
Cuba	-	5	2	-	7
Sweden	1	2	2	1	6
Other countries	*Countries with less than 5 articles*				36

Legend: N, total number of manuscripts. Total number of revised manuscript was 225.

Table 3. Classification of manuscript according to: Fields of research.

Field	N	%
Caries	46	20.5
Materials	36	16
Endodontic	34	15
Surgery	29	12.5
General	34	14.5
Periodontics	17	7.5
Soft Tissue Lesions	8	3.5
Dental unit water lines (DUWL)	4	1.7
Temporomandibular joint (TMJ)	6	2.5
Whitening	4	2
Orthodontics	3	1.8
Cytotoxicity	4	1.8

Legend: N, total number of manuscripts. Total number of revised manuscript was 225.

Table 4. Frequency distribution of articles by ozone generators and specifications.

Generator	N	%	O_3 (µg/mL)	O_2	Flow Rate
Healozone	75	65	4.2	Ambient air	650 mL/min
Ozonytron	18	14.5	Unclear	Air/Pure O_2	Unclear
Prozone	12	10.5	0.2	Ambient air	2 L/min
Others	13	11	Not specified		

Table 5. Frequency and relative frequency distribution of articles by field of research and results.

Field	N	Results (%) *		
		G/S	*G/NS*	*NS*
Caries	46	71	29	
Materials	36	86	14	
Endodontic	34	77	23	
Surgery	29	89	11	
Periodontics	17	75	25	
Soft tissue lesions (STL)	8	88	12	
Temporomandibular Joint (TMJ)	6	100	-	
Dental unit water lines (DUWL)	4	100	-	
Whitening	4	50	50	
Orthodontics	3	67	33	
General	38			
Total	**225**	**77**	**23**	

Legend: N, total number of manuscripts. * *Percent of Results:* ***G/S*** *Good/Significant,* ***G/NS*** *Good/non-significant,* ***NS*** *non-significant.*

Clinical Expertise: Dental professionals' Ozone Clinical protocols – Parameters

Due to logistical and time constraints, the collection of clinical protocols on ozone therapy applied by the majority of dental professionals, worldwide, fields of application, etc. was limited to direct contacts with individual dentists, associations, educators and trainers. Information pertaining to ozone concentration, oxygen source and modes of application were gathered in order to draw a general guideline that is mostly followed by the dental professionals.
The majority of dentists use ozone gas and water (mostly combined), few others use ozonated water only. The following are the reported concentrations used:

i. Ozone gas: Concentration 10-100 µg/mL. Flow rate: 30-1 000 mL/min. Application time: 30 s to 5 min.
ii. Ozonated water: Concentration 4-20 µg/mL; Volume: Unclear.
iii. Ozonated oils peroxide value (PV): Unclear.

3. Data Analysis

3.1. Group Gas only

Table 6. Frequency and relative frequency distribution of articles by country, year of publication, results and type of ozone gas generator.

Country	1999 2004	2005 2010	2011 2015	2016 2017	N 118	%	Results (%)[1]			Generator[2]		
							G/S	G/NS	NS	H	Oz	P
1. Turkey	-	4	20	8	32	26.5	69	31		9	13	4
2. U.K.	20	2	3	1	26	22.5	92.5	7.5		26		
3. Germany	1	4	1	3	9	7.5	44.5	55.5		8		
4. Italy	-	4	1	2	7	6	71.5	28.5		3	1	
5. Sweden	1	2	2	1	6	5	66.5	33.5		4		1
6. Switzerland	-	5	1	-	6	5	20	80		5		1
7. Brazil	-	-	1	3	4	3.5	25	75			1	
8. Egypt	1	-	2	-	3	2.5	66.5	33.5		2	1	
9. Australia	-	2	1	-	3	2.5	33.5	66.5		2		1
10. Croatia	-	2	1	-	3	2.5	100	-		3		
11. Portugal	-	-	3	-	3	2.5	100	-		1		2
12. U.A.E.	-	2	-	-	2	1.5	100	-		2		
Total	**23**	**27**	**36**	**18**	**104**		**67%**	**33%**		**74***	**17***	**12***
Not listed: countries with 1 article only (14 manuscript)							-	-		65%	15%	10%

Legend: N, total number of manuscripts 118 (include 14 manuscripts of the non-listed countries) 1) *G/S Good/Significant, G/NS Good/non-significant, -NS non-significant. 2) Type of generator:* ***H****: Healozone;* ***Oz****: Ozonytron;* ***P****: Prozone.* U.K., United Kingdom; U.A.E., United Arab Emirates, ***** *Including the not listed article.*

3.1.1 Generators used in group Gas only

1. *The Healozone*[6] generator was used in 65% of the ozone gas only studies - Table 6. For safety reasons, this system generates ozone gas only when a hermetic seal of the treatment area is achieved by using a silicone cap on the delivery handpiece. It generates ozone gas from dry ambient air at a fixed concentration of ~4.2 µg/mL and ~650 mL/min flow rate. The application time varied from 10 s to 180 s yielding a total dose of (0.06 – 8.20) mg ozone gas. In 57/74 studies (77%) good/significant results were noted, whereas the remaining 23% revealed a combined good/non-significant and non-significant results.
Only one *in vivo* study, which showed good/significant results, used a second version of the Healozone which generates ozone gas from dry ambient air as the first version) or from pure oxygen at a fixed concentration of 32 µg/mL. Application time was 120 s yielding a total ozone dose of ~128 mg.

2. *The Ozonytron*[7] was used in 15% of the ozone gas only studies – Table 6. This system generates a plasma phase, including ozone, from the air surrounding the treatment area via an electro-magnetic field. Other models generate ozone from pure oxygen. According to the technical specifications from the manufacturer's website, as well as the ozone concentration values and measurement units, it is difficult to specify with accuracy the ozone concentration that can be achieved with these units. The claimed ozone gas concentration values, in our opinion, are either exaggerated or misrepresented, a fact confirmed by the following concentration values as indicated in the manufacturer's website:

"Ozone concentration when using the ozone injector:
- *Flowing in with 1 L/min*
- *Using atmospheric oxygen: 800 ppm to 22 000 ppm*
- *Using 99.5 % medically pure oxygen from the gas bottle: 3 000 bis 100 000 ppm – (6 – 200) g/L*

Converting ppm into µg/mL (refer to sidebar 2), it is clear that there is a misrepresentation of the ozone concentration and the measurement units used.

Sidebar II

Converting ppm into µg/mL 800 ppm to 22 000 ppm is equal to about 1.6 µg/mL – 44 µg/mL. 3 000 ppm to 100 000 ppm is about 6 µg/mL – 200 µg/mL. 6 – 200 g/L is equal to 6 000 – 200 000 µg/mL.

The majority of the articles citing the use of the ozone injector, the Ozonytron, the ozone concentration could not be easily interpreted as the authors reported it in general terms such as *"According to the manufacturer's instructions", "The system was operated at 5N intensity in accordance with the manufacturer's instructions",*

"O_3 was delivered at 100 % for 40 s with peristaltic motions, as recommended by the manufacturer", "Gas Topical application. Activated oxygen ozone) concentration of 30 %", or "In accordance with the manufacturer's instructions, at 100% volume for 40 s".

Of the 17 studies, 65% showed good/significant results and 35% combined good/non-significant and non-significant results.

3. *The Prozone*[8] was used in 10% of the ozone gas only studies – Table 6. This system generates ozone from ambient air at a fixed ozone concentration of ~0.25 µg/mL and 2 L/min flow rate. Time of application varied between 6 s and 240 s yielding a total applied ozone dose of 0.08 mg – 2 mg. Of the 12 studies, 50% showed good/significant results and 50% combined good/non-significant and non-significant results.

By comparison to medical ozone generators where only pure oxygen is used to generate ozone gas, these dental systems operate on ambient air and produce low ozone concentrations. A reason why most of the research authors used these models is that they are CE medical device certified, which is a prerequisite in the European Union where the vast majority of research was conducted.

This discrepancy between medical and dental ozone systems is unclear. It's highly recommended that dental ozone manufacturers follow the technical specifications commonly used in medical ozone systems which reference pure oxygen sources and a large spectrum of ozone gas concentrations.

Summary of ozone parameters used in group gas only between research and clinicians:

Group O_3 gas only	Research	Dentists	Results %		
			G/S	G/NS	NS
Concentration (µg/mL)	0.2 – 4.2	10 - 100	67	33	
Oxygen source	Ambient air	Pure oxygen	-	-	-
Dose (mg)	0.06 – 8.2	3 - 120	-	-	-

Legend: Results: G/S, Good/Significant; G/NS, Good/non-significant; NS, non-significant.

A clear divergence is evident between "ozone gas only" research studies and clinicians reference oxygen source and ozone concentrations. It is noteworthy to mention that dentists follow the same specifications and parameters as used by medical doctors in topical applications, which is also well reflected in medical research covering this particular field of application, whereas the dental research in "ozone gas only" is somehow following a different path.

It is with hope, that future dental ozone studies take into consideration this finding. We would also hope that authors consider following the same guidelines, specifications and parameters as used in medical topical applications. We suspect that the negative results (33%) would be vastly improved. It is also anticipated that dental ozone manufactures provide reliable and improved systems specifically designed for dental applications and be CE certified in order to be safely and legally used in dental ozone studies.

3.2. Group ozonated water only

Table 7. Summary of articles by country, Field, and Results.

Country	N	Country	N	Field	N	Field	N	Results %		
								G/S	G/NS	NS
Japan	10	Switzerland	4	Periodontics	13	DUWL	4			
India	8	Egypt	**3**	Surgery	9	Caries	3			
Germany	7	China	**3**	Endodontic	7	Soft tissue lesions	2	85	15	
Brazil	6	U.K.	**2**	Materials	6	TMJ	1			
Turkey	5	**53 articles***		General	6	Cytotoxicity	1			

Legend: N, total number of manuscripts. * Including the not listed article (countries with 1 article only). DUWL, Dental unit water lines; TMJ, Temporomandibular Joint; UK, United Kingdom. Results: G/S, Good/Significant; G/NS, Good/non-significant; NS, non-significant.

Lower negative results were noted in group “ozonated water only” (15%) – Table 7 - compared to group “ozone gas only” (33%) – Table 6.

Table 8. Ozonated water concentration used in the studies and results.

Low concentrations µg/mL	N	%	Hight concentrations µg/mL	N	%
< 0.1	10	19	4-6	12	23
< 2	6	12	8-15	8	15
			16-25	17	32
Total	16	31		37	69
Results %	G/S: 50 G/NS-NS: 50		Results %	G/S: 89 G/NS-NS: 11	

Legend: N, total number of manuscripts. %, percent of the total number of manuscripts analyzed (53). Results: G/S, Good/Significant; G/NS, Good/non-significant; NS, non-significant.

It was further observed that 19% of the total number of studies used less than 0.1 µg/mL concentration, and 12% used less than 2 µg/mL, yielding 50% combined negative results in comparison to 11% in other studies where a higher concentration of (4-25) µg/mL was used.

Unlike the observed discrepancy in ozone parameters between clinicians and research in group “ozone gas only”, there is a concordance between clinical applications and research findings in group “ozonated water only”.

It is thus recommended that future studies use medium to high ozonated water concentrations of (4-25) µg/mL which are commonly used in medical topical applications and by dental clinicians.

3.3 Group ozonated oils

Table 9. Summary of articles by Country and Field.

Country	N 30	Field	N
Italy	7	Surgery	10
India	6	Antibacterial	6
Egypt	5	Periodontics	4
Cuba	4	Endodontic	3
Brazil	3	Soft tissue lesions	2
Countries 1 article each	5	Cytotoxicity	2
		Caries	1
		Materials	1
		Hyper-sensitivity	1

Legend: N, total number of manuscripts. Total number of manuscript analyses was 30.

Table 10. Concentrations and Results.

Concentration mEq O_2/kg	**N**	**Results % [G/S]**
~ 1 300	4	**100**
590	1	
0.025-0.5%	1	
Not specified	24	

Legend: N, total number of manuscripts. G/S, Good significant. Total number of manuscript analyses was 30.

The major positive result noted in ozonated oils studies is strongly suggestive of their usefulness in dental applications, as also observed in topical medical applications. Additionally, the lack of ozonated oils concentration specification in the majority of the dental studies was observed. The role and responsibility of ozonated oils producers to label their products with the peroxide value[9] (in mEq O_2/kg or in mmol O_2/kg) is vital in order to compare different vegetable oils and concentrations best suited for dental applications.

3.4 Group ozone gas and ozonated water

A striking observation is the very low number of studies where both ozone gas and ozonated water were used. In medical topical applications studies, it's only normal to use both gas and water, and the positive results observed in the 14 dental studies is proof that both gas and water should be used instead of only gas or only water.

In our opinion, the common practice in clinical applications of the combined use of gas and water when applicable should be the norm in future dental research studies, as well as the use of medium to high ozone concentrations.

Table 11. Summary of articles by Country or Field.

Country	N	C/S[1]	Field	N
Egypt	3	C	Endodontic	5
Brazil	3	S	Materials	2
Turkey	3	S	Cytotoxicity	2
Germany	2	S	TMJ	1
Cuba	1	C	Caries	1
USA	1	C	Soft tissue lesions	1
Poland	1	S	Periodontics	1
			Surgery	1
Total	**14**		**Total**	**14**

Legend: N, total number of manuscripts. [1]***C/S***: ***C****ombined or* ***S****eparate use of ozone gas and/or water*. TMJ, Temporomandibular Joint.

Table 12. Concentrations and Results.

Concentration µg/mL		**N**	**Results %**	
			GS	**G/NS**
Ozone gas	*Ozonated water*			
4.2	4	5	**93**	**7**
0.2-53	1-20	2		
6-20	20	2		
60	25	1		
40	8	1		
Not specified		3		

Legend: N, total number of manuscripts. Results: G/S, Good/Significant; G/NS, Good/non-significant. Total number of manuscript analyses was 14.

3.5. Group Topical – Systemic ozone application

Table 13. Summary of articles by Country, Field, Application Mode and Results.

Country	Field	N	Application Mode	Results % [GS]
Ukraine	Surgery	2	O_3 water + IV O_3 saline	**100**
Egypt	Surgery	1	Not specified	
Russia	Surgery	1	O_3 water + IV O_3 saline	
Cuba	TMJ	1	IA *vs.* Rectal + IA	
Turkey	Surgery	1	Intraperitoneal + O_3 gas	

Legend: N, total number of manuscripts. TMJ, Temporomandibular Joint. IV, Intra Venous; IA, Intra articular. Results: GS Good/Significant. Total number of manuscript analyses was 6.

In light of the increasing evidence and research in oral-systemic health links, it is essential that medical and dental health professionals, especially researchers, join efforts and conduct more studies in order to elucidate the usefulness of ozone therapy in chronic inflammatory diseases both oral and systemic.

This holistic health approach would greatly benefit patients suffering from chronic oxidative stress where ozone therapy is highly indicated.

In our opinion, there is an urgent need to conduct more studies on this subject which will take ozone therapy as a whole to a totally new level, especially that adult chronic periodontitis is considered one of the most common chronic inflammatory diseases affecting several systemic conditions, and vice versa.

3.6. Group ozone injections

The promising positive results seen in these dental studies, and by comparison to the very large number of published articles in medical ozone therapy with the highest grade of evidence-based medicine in vertebral-paravertebral ozone injections, warrant more research in temporomandibular joint (TMJ) and related muscles. As in the case of chronic periodontitis affecting a large number of the population, temporomandibular joint disorders is also considered one of the most common skeletal inflammatory and degenerative conditions. Future research in this field would help dental clinicians to distinguish between the beneficial effects of the TMJ intra-articular and the para-articular ozone injections, as well as the topical applications as seen in some studies where ozone gas was topically applied over the affected TMJ area (Table 14).

Table 14. Summary of articles by Country, Field, Application Mode and Results.

Country	Field	N	Application Mode	Results %
Egypt	TMJ	3	O_3 gas and/or O_3 water	**[G/S]** 100
Turkey	Ortho	1	O_3 gas	

Legend: N, total number of manuscripts. TMJ, Temporomandibular joint. Ortho., Orthodontics. Results: G/S Good/Significant. Total number of manuscript analyses was 4.

4. Discussion

It is indisputable that ozone therapy in dentistry is growing and is being used by an increasing number of dentists worldwide. The clinical experiences and treatment outcomes are adding significant amounts of knowledge. Dental research should follow and support dental professionals in their daily practice of ozone therapy. As well, dental professionals will benefit from the experiences of our medical colleagues.

Most importantly, the discrepancy noted between research and clinicians in ozone gas specifications and oxygen feed sources is significant. A major contributing factor to this discrepancy is the available dental ozone gas systems offered to researchers, most of which operate on ambient air and generate low ozone gas concentrations.

In addition, it is fundamental that ozone dental units be designed with a larger spectrum of gas concentration and be certified for use in research. There is a large choice of commercially available medical units. However, the average cost of these systems might be prohibitive for dental use.

In 15% of the ozone gas articles, the concentration and flow rate were not clearly specified, thus of little or no value for clinicians. It is paramount that authors measure the concentrations of the generated gas, and not solely rely on manufacturers' recommendations.

Similarly, the peroxide value (PV) of the ozonated oil products should be tested by researchers in all instances. The majority of ozonated oils articles did not specify the PV, which is essential for clinicians to choose the appropriate concentration according to the clinical case.

We cannot stress enough about the need and importance of future dental research studies incorporating both ozone gas and water, as well as ozonated oils when applicable. These therapies are what the majority of dentists apply in their practice and it might very well improve the overall positive and significant results in research.

Dental ozone research ought to change its course to meet the expectations of clinicians. Research needs to explore new and different studies than the conventional and well-studied antimicrobial potential of ozone. Most importantly the direct ozone application on pulp exposures, whether due to caries, trauma or iatrogenic, and to evaluate the potential of dentin generation and pulp tissue cytotoxicity according to the ozone form and applied dose.

The assistance and cooperation of our medical colleagues is well appreciated, especially in conducting more studies in the field of oral-systemic links.

Lastly, ozone equipment manufacturers have a major role to play in the evolution of dental ozone research and clinical ozone practices.

5. Change History

SOP no.	Effective Date	Significant Changes	Previous SOP no.
ISCO3/QAU/00/23	15/02/2018	First Draft. Manuscript written by the working group, edited.	First version
ISCO3/QAU/00/23	05/02/2018	Draft 2 edited according suggestion of the working group and summited to the ISCO3 voting	Amended draft

6. Document Records

	Name	**Title**	**Signature**	**Date**
Author	Fadi Sabbah	Elected vice- president D.DS.		10/02/2018
Co. Authors / Reviewer. Working group	Dr. Eric Zaremski	External expert.		15/02/2018
	Dr. Nory Bazzano Mastelli	ISCO3 Member		15/02/2018
	Dr. Carlos Nogales	ISCO3 expert group.		15/02/2018
Edition / Correction	Gregorio Martínez-Sánchez	Elected president Ph.D.; Pharm. D.		5/04/2018
Authoriser / Approved	ISCO3 Board 2015-2020			23/04/2018

Appendix: Articles Consulted

Some selected unpublished articles without formal citation *(highlighted in yellow)* were collected from scientific ozone meetings**.**

Ozone Gas

1. Influence of Ozone on Oxidation of Dental Alloys. Suzuki/Oizumi/Furuya/Okamoto/Rosenstiel. International Journal of Prosthodontics Year 1999 Volume 12, Issue 2.
2. Chemical treatment of machined titanium surfaces. An in vitro study. Krozer A, Hall J, Ericsson I. Clin Oral Implants Res. 1999 Jun;103):204-11.
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