Sterilization with ozone in health care: an integrative literature review*

OZÔNIO NA ESTERILIZAÇÃO DE PRODUTOS PARA ASSISTÊNCIA À SAÚDE: REVISÃO INTEGRATIVA DA LITERATURA

OZONO EN LA ESTERILIZACIÓN DE PRODUCTOS PARA ATENCIÓN DE SALUD: REVISIÓN INTEGRADORA DE LA LITERATURA

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ABSTRACT

The objective of this integrative literature review was to find evidence to support using ozone as a sterilizing agent for health products. The search was performed on the following bases: MEDLINE, SCOPUS, COCHRANE, COMPENDEX, INSPEC and ENGINEERING RESEARCH DATABASE; using ozone and sterilization as descriptors. Five articles were found between 1990 and 2008, which tested ozone as a sterilizer. All studies used the same type of investigation (experimental laboratory study) and achieved sterilization with ozone, but with different scopes and products, besides using different methodological procedures. Considering the ever-growing technology for new products, with the vast range of forms and materials, the findings point at ozone sterilization as a promising method, but still in an initial phase of investigation. Further experimental studies are needed to provide broader evidence regarding the possibilities and limitations of ozone sterilization.

DESCRIPTORS

Ozone
Sterilization
Nursing

RESUMO

Estudo de revisão integrativa da literatura com o objetivo de buscar evidências que subsidiem a incorporação do ozônio como agente esterilizante de produtos para saúde. A busca foi realizada nas bases MEDLINE, SCOPUS, COCHRANE, COMPENDEX, INSPEC E ENGINEERING RESEARCH DATABASE, utilizando-se os descritores *ozone* e *sterilization*. Foram obtidas cinco publicações, entre 1990 e 2008, que testaram o ozônio como esterilizante. Todas utilizaram o mesmo tipo de investigação (experimental laboratorial) e alcançaram esterilização pelo ozônio, porém com variados escopos e produtos testados, além de diversos procedimentos metodológicos. Tendo em vista a incessante tecnologia de novos produtos, com ampla variedade de conformações e matéria-prima, os achados denotam o ozônio um método promissor, porém ainda em fase inicial de investigação. Mais estudos experimentais ainda são necessários, de maneira a subsidiar evidências mais amplas sobre suas possibilidades e limitações.

DESCRITORES

Ozônio
Esterilização
Enfermagem

RESUMEN

Estudio de revisión integradora de literatura objetivando buscar evidencias que respalden la incorporación del ozono como agente esterilizante de productos para la salud. La búsqueda se realizó en las bases MEDLINE, SCOPUS, COCHRANE, COMPENDEX, INSPEC y ENGINEERING RESEARCH DATABASE, utilizándose los descriptores ozone y sterilization. Se rescataron cinco publicaciones entre 1990 y 2008 que testearon al ozono como esterilizante. Todas utilizaron el mismo tipo de investigación (experimental laboratorial) y consiguieron la esterilización mediante el ozono; sin embargo, con variados objetivos y productos probados, además de diversidad de procedimientos metodológicos. Teniendo en cuenta la alta tecnología de nuevos productos, con amplia diversidad de conformaciones y materias primas, los hallazgos determinan al ozono como método promisorio, no obstante que aún esté en fase inicial de investigación. Se necesitan más estudios experimentales, para respaldar con evidencias ampliadas sus posibilidades y limitaciones.

DESCRIPTORES

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INTRODUCTION

Choosing the appropriate method to process products used in health care delivery is essential to ensuring that potential pathogens that cause infections are not transmitted to patients[1-2]. The quality of processing is the foundation of preventing infections associated with certain procedures through the microbial reduction or destruction in products used, as well as the maintenance of a product's functionality and integrity[3].

Sterilizing refers to the processing stage that destroys or eliminates all forms of microbial life from the surface of articles, which may be performed through physical or chemical processes[4]. The continuous search for low temperature sterilization technologies is due to the need for adequate sterilizing agents related to the physical-chemical characteristics of products launched in the market, seeking the convenience of greater speed in processing, in addition to environmental issues in comparison to the methods normally used[1,4]. The low-temperature sterilization processes currently available include: ethylene oxide, hydrogen peroxide plasma, low-temperature steam and formaldehyde (LTSF), gamma radiation, electron beam technology, liquid chemical sterilizing (LCS) and, more recently, ozone (O_3)[1,5].

A Canadian company (TSO3. Inc®) developed a process in 2003 using O_3 as the single sterilizing agent[6]. Such a process was approved by both Health Canada and the Food Drug Administration (FDA) in the United States because it was considered safe and fast, and also an economical alternative to low-temperature sterilization[6]. The efficiency of this process is established when it achieves the Sterility Assurance Level (SAL) of 10^{-6} [7].

O_3 is present in the environment and is naturally via oxygen in the stratosphere through the absorption of the sun's ultraviolet radiation[8]. It can also be mechanically produced, such as in photocopy machines[9]. When O_3 is obtained through electrochemical technology, it is an alternative for breaking down resistant organic compounds, such as dyes from textile effluents, pesticides, and waste from the paper industry[7].

Even though not legally recognized in many countries, including Brazil, O_3 has been used as a therapeutic alternative to care for various types of diseases under different forms of applications, topical and systemic, since the beginning of the 20th century[10]. Many other uses are known: antimicrobial in the treatment, storage and processing of food genders[11], purification or treatment of water and sewage, sterilization of water bottles[6], and decontamination of environments such as hotel and hospital rooms[12].

O_3 is easily soluble in water and highly oxidative when in a gaseous state. This characteristic, combined with its solubility, makes it an excellent candidate to be used as a sterilizing. Its oxidative capacity is greater than that of hydrogen peroxide and peracetic acid, which makes its stronger and more efficient as a sterilizing[6].

The guarantee that O_3 sterilizes is not sufficient, however, for its broad application in products used in health care. It is currently a challenge to always assess new technologies based on scientific evidence in order to ensure a better cost-benefit relationship, especially in relation to the absence of adverse effects for patients and professionals[13]. This integrative literature review evaluates whether there is sufficient data in the scientific literature to support the use of O_3 as a physical-chemical-sterilizing agent for health products.

METHOD

An integrative literature review is one of the methods used in evidence-based practice that includes the analysis of studies relevant for decision-making and improving care practices[14]. It enables the synthesis of knowledge acquired on a given subject and indicates gaps that need to be filled in with further research.

Even though not legally recognized in many countries, including Brazil, O_3 has been used as a therapeutic alternative to care for various types of diseases under different forms of applications, topical and systemic, since the beginning of the 20th century.

The literature search was conducted through July 2010 without restrictions concerning language or period of publication in the following databases: MEDLINE, SCOPUS, COCHRANE, COMPENDEX, ENGINEERING RESEARCH DATABASE and INSPEC using the descriptors *ozone* and *sterilization* from the Medical Subject Headings Section (MeSH). Only primary studies addressing the use of O3 as a sterilizing agent for health products were included. These were selected by the title and abstract and only those that met the inclusion criteria were fully read. Papers identified in more than one database were analyzed only once. Figure 1 presents the search results.

The included studies were classified according to the identification of the publication (author(s), title, periodical, year, country of origin, language) and data from the experiment concerning: scope, type of study, methodological procedures, results, considerations of this review, conflicts of interest, and score concerning quality of methodological rigor.

In order to assess methodological rigor we took as a reference point the best quality to be expected concerning studies of this nature[15-16], which implies: a) laboratory experimental design; b) information concerning the process of sterilization with O_3 (concentration, humidity, time, temperature, vacuum and ventilation), description of methodological procedures as evidence of: direct inoculation of resistant microorganisms (spores) on the

products, culture and reading of material of experimental groups (which were sterilized by O_3), positive control (without sterilization) and negative control (sterilization with approved equipment, preferably a steam autoclave); c) conflicts of interest (studies conducted by manufacturers). We considered 10 the maximum score, which was reduced, as the studies did not meet the criteria or incompletely met criteria previously described.

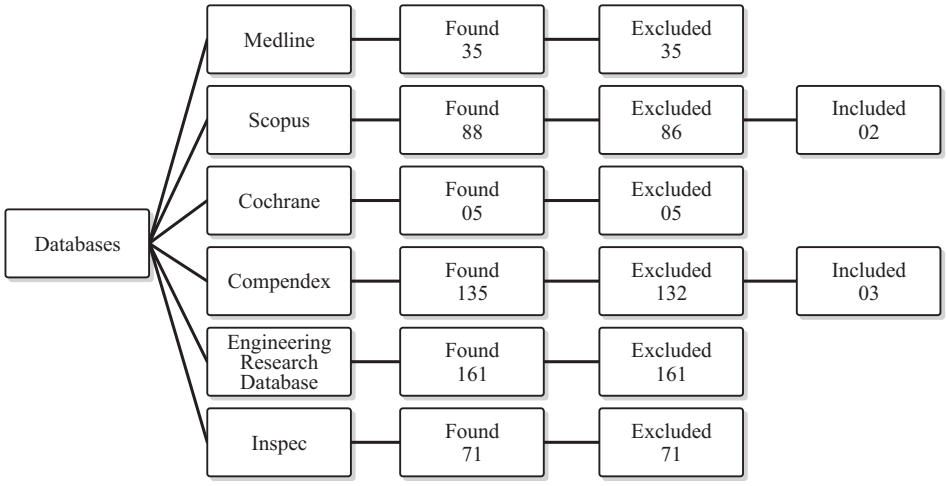

Figure 1 – Diagram of the selection process of papers in the databases

RESULTS

Five studies from the 1990s and later that met the inclusion criteria were analyzed. The authors are from different professions (medicine, chemistry and water analysis-E2, Engineering-E5, E3), the professions of the authors of two studies (E1 and E4) were not possible to identify. The studies were carried out in the United States (E1), Canada (E5), Japan (E2, E3) and Russia (E4). The thematic fields of the periodicals that published these studies were engineering (E3, E4), chemistry (E2), hospital-acquired infection (E5) and biological sciences (E1). All the studies used the same study design (laboratory experiments) and achieved sterilization through O_3, though with varied scopes of use and products tested, in addition to a diversity of methodological procedures.

Scopes ranged from sterilization and/or capacity to inhibit bacteria (E1 to E5) including the relationship among time, temperature and humidity (E1, E3), comparisons of microbial inhibition among products in different shapes (E2, E3), penetration in rigid lumens (E5), release of toxic substances due to the reactions of products to O_3 (E2). High concentrations of O_3 resulted in toxic levels of residues on materials and procedures were required to eliminate them (E3).

The following products were tested: a self-rotating drill (E1); polymers – hydrophilic polysulfone (PS), hydrophilic polycarbonate (PC), hydrophilic polyvinylidene fluoride (PVDF) (E2); synthetic polymers of different characteristics (E3); stainless steel of various levels of roughness (E3); Petri dishes (E4); and rigid stainless steel lumens (E5). Among the results, the conclusion is that O_3 causes reactions on polymer material with the release of toxic substances, though this is also observed in other sterilization methods such as steam and ethylene oxide. Differences of diffusion, reaction, and bacterial inhibition capacity occur depending on the type of product (E3). The sterilization of lumens was obtained using rigid stainless products with 45 to 70 cm of length and 0.5 to 4mm of diameter. The studies analyzed in this review do not report any sterilization action in the case of flexible lumens.

Sterilization was obtained over different periods of time, from 3 to 5 minutes, directly proportional to the concentration of O_3 (3,000 to 30,000ppm) and humidity; one of the studies mentions equipment already available commercially, but does not report its parameters.

All the methodological procedures used microbiological contamination tests by inoculation on material with standard microorganism: E1 used *B.subtilis*, E2, E3 and E5 used *B. stearotermophilus*, and the E4 study used *B. Anthrax*. Only E4 and E5 used the bioburden standard (10^6). Positive and negative controls were not presented for E1 while E3 mentioned only negative control. Only E5 reports the duration of contact of the contaminant with the material before sterilization.

Scores attributed to the studies according to the established criteria were: 5 (E1), 6 (E3, E4), 8 (E2, E5). Hence, scores range from 5 to 8 according to methodological criteria of reference procedures for this kind of study. In this respect, the studies considered the best were E2, which sterilized the material with polymers and E5, which tested rigid stainless lumens (score 8). The worst was E1, which tested a self-rotating drill (score 5). A synthesis of the studies is presented in Table 1.

Table 1 – Synthesis of the studies selected from the databases – São Paulo, SP, Brazil – 2010

E1 - Massuda S, Ieee F., Kiss E, Ishida K, Asai H. Ceramic-Based Ozonizer for High-Speed Sterilization. Ieee transactions on industry applications 1990 Jan;26(1):36-41.			
Scope	**Methodological procedure**	**Results**	**Considerations**
Testing conditions for high-speed sterilization of dental products with O_3 gas.	- Sterilizer: O_3 gas in different concentrations, times of exposure, temperatures, humidity, with dry and wet products. - Tested product: self-rotating drill contaminated with *B.subtilis* - Negative and positive controls are not mentioned	- Sterilization obtained with a concentration of 20,000-30,000ppm of O_3, 50ºC, 3-5 minutes of exposure, relative humidity at 80%, total time of the process 14-15min; - humidity is essential for O_3 to get into contact with the product - reduction of residual O_3 at the maximum of 0.5 pg/cm^2 by aeration with clean air at 50ºC at the end of the process.	*B.subtilis* is not usually used in O_3 sterilization; - the contamination process and microbial recovery are not described; - other products from the health field need to be validated; - Conflict of interest: Equipment tested by the manufacturers.
E2- Shintani H, Suzuki E, Sakurai M. Determination of compounds inhibiting bacterial growth in sterilized medical devices. Chromatographia 2003 Aug;58(3-4):193-9.			
Scope	**Methodological procedures**	**Results**	**Considerations**
Identifying whether bacterial inhibition occurs by the release of compounds through polymer material after sterilization with O_3 gas.	- Sterilizer: O_3 gas, 3,000ppm, 35C0, 20-50 min, relative humidity at 80% . - Tested products: polymers (PS, PC, PVDF). - Positive control of bacterial growth: yes - Negative control: steam autoclave.	- Significant microbial inhibition on PS after sterilization with O_3, in contrast with mild inhibition with steam; - Differences on bacterial growth among types of polymers; - New compound is formed on PS in the O_3 sterilization; - Synthesis of new compound on PS in the O_3; - The potential of O_3 to reduce oxygen may be accounted for by the formation of the new compound on the PS; -The new compound may have inhibited microbial growth given the better results obtained in the case of PS.	-Microbial load below 10^6. -Conflict of interest: There is none.
E3 Sakurai M, Takahashi R, Fukunaga S, Shiomi S, Kazuma K, Shintani H. Several Factors Affecting Ozone Gas Sterilization. Biocontrol Science 2003;18(2):69-76.			
Scope	**Methodological procedures**	**Results**	**Considerations**
Evaluating the relationship between the concentration of O_3 gas, relative humidity, temperature and differences in the D value of medical products and also studying whether O_3 gas is affected by differences in the composition of medical products.	- Sterilizer: ozonizer (M6R), 15,000 ppm, 25ºC, time of exposure varied according to material, relative humidity 80% to 90%. - Tested products: synthetic polymers with different characteristics and stainless steel of various levels of surface roughness. - Positive control: does not mention. - Negative control: steam autoclave	- The greater the concentration of the O_3 gas, relative humidity or temperature, the lower is the D value; - Time of sterilization inversely proportional to the O_3 concentration, relative humidity and temperature; - The more hydrophilic the polymer material, the higher the D values; - D value was higher in the case of stainless steel; - Roughness of stainless steel surface did not cause any significant difference in D values, unlike its components (Ni, Fe); - Higher D values on stainless steel can be explained by the quantitative difference of mineral components that may destroy O_3 gas; - Comparing ATCC 7953 with ATCC 12980, the first should be used as biological indicator for O_3 sterilization because it has been more resistant.	- Microbial contamination population below 10^6; it does not report the time of contamination contact nor negative control. - Conflict of interest: Three authors work in the industry, no specification.
E4 Buranov SN, Karelin VI, Selemir VD. Sterilizing effect of ozone on live spores of anthrax bacillus. Russian Federal Nuclear Center 2005.			
Scope	**Methodological Procedures**	**Results**	**Considerations**
Showing the effect of O_3 on B. Anthrax spores.	- Experiment with O_3 gas, concentration of 20.000 ppm, different periods of exposure (5, 10, 30 and 60 min.) - Positive control: yes - Negative control: steam autoclave.	- B. Anthrax destroyed when exposed to O3 for 60 min. - B. stearothermophilus undetectable in exposures of $\geq$ 5 min.	- Test of microorganisms' resistance to O_3 was performed. - It did not constitute a sterilization process - Conflict of interest: there is none.

Continue...

E5 Dufresne S, Leblond H, Chaunet M. Relationship between lumen diameter and length sterilized in the 125L ozone sterilizer. Am J Infect Control 2008 May;36(4):291-7.			
Scope	**Methodological Procedures**	**Results**	**Considerations**
Validating sterilization of lumens with O_3 gas.	- Sterilizer: O3 gas (TSO_3 Inc®, 125L) - Tested products: stainless steel lumens used in the fabrication of hypodermic needles (0.5-4 mm diameter and 45-70cm length) and semi rigid uteroscopy - Positive control: yes - Negative control: yes	- All the lumens with the exception of one with 1mm of internal diameter and 50 cm of length did not present bacterial growth; - Lengths appropriate for sterilization according to the lumen's diameter: lumens ranged from 45 and 70 cm, according to the diameter (0.5 mm x 45cm; 1mm x 50cm; 2mm x 57,5; 3mm x 65cm; 4mm x 70cm). - No growth was observed in the uteroscopy, a medical device difficult to sterilize, after 14 days of incubation before perform effect the three tests.	- Conflict of interest: there is none.

DISCUSSION

The practices recommended by the Association of periOperative Registered Nurses (AORN) concerning the sterilization of health products assume that O_3 is a strong oxidant, which can enable the construction of an effective low-temperature sterilization system[17]. However, the relation between microbial load and time, concentration, humidity and capacity of O_3 diffusion are essential aspects to analyze and define the sterilizing capacity of O_3[18]. Other aspects include the maintenance of product integrity and toxicity both in relation to its reaction with products and occupational risk given the release of the agent into the environment.

If, as it seems, there are no doubts concerning the O_3 sterilization proprieties, many questions remain concerning its advantages over other methods already available in the market, especially for thermo-sensitive products, whose diversity offers many levels of difficulty from diffusion capacity to reactions to the agent posing a risk to the product's integrity and release of toxic substances.

Even though the methods already available present limitations and do not encompass all this diversity, identifying the advantages and limitations of sterilization with O_3 is needed. One of its most acknowledged advantages is its cost-effectiveness; it does not require inputs because oxygen is used to produce O_3. In relation to the products, it is known that those with narrow lumens are more challenging to sterilize than those with long lumens[13]. Even though the diffusion of O_3 in lumens of various diameters and lengths were proven in this review, these were composed of rigid stainless steel (E5), that is, they can also be sterilized by steam. The greatest challenge would be to prove its efficiency with flexible lumens. In this context, the type of material composing the product is an additional issue.

Diverse thermo-sensitive products are composed of polymers. Even though E2 obtained significant microbial inhibition in PS and PC in contrast to mild inhibition on PS through steam, complete survival occurred in PVDF. Additionally, compounds were released: Bisphenol A by PC and PS, and Bisphenol S and polymer 4-chloro-4¢-hydroxydiphenyl by PS. The authors suggest that the ample potential of O_3 to reduce oxygen may have been the cause and also inhibited microbial growth given the better results obtained by PS. E3 also reports release of Bisphenol A by polyester polymer (PES), which may have contributed to inhibiting bacterial growth when cultivated in casein soy. Nevertheless, formation of compounds from polymers has also been obtained by other methods (O_3, steam, hydrogen peroxide, gamma radiation, and electron beams).

Bisphenol is a known toxic compound. The authors of the E3 study state that the polyester used in hemodialysis membranes may be harmful in renal therapy when sterilized. In turn, a study that sought to determine whether *Saccharomyces cerevisiae* released estrogen cultivated it in PC bottles, which were later autoclaved, and concluded that the conditioned estrogenic substance was not a product of grown yeast but it was drawn out of the PC bottles themselves during the autoclave process. This substance was analyzed and the purified final product was identified as Bisphenol A, which raised the possibility that the estrogenic activity under the form of Bisphenol may have an impact on the outcome of using an autoclave on PC bottles[19]. Another study exposed placenta tissue to Bisphenol A and obtained as a result the possibility of very low doses of Bisphenol A inducing apoptosis (2-3 times) and necrosis (1.3-1.7 times). Additionally, Bisphenol A significantly increased the Tumor Necrosis Factor – Alpha (TNF-alpha)[20].

Therefore, the sterilization of polymers, both through O_3 and other methods, can release toxic substances. Different types of polymers offer lower or higher resistance to O_3. Study E3 reported that hydrophilic polymers presented higher density compared to the hydrophobic ones; thus, the first may permit deeper penetration of spores and result in greater resistance to the sterilizing agent. Another possibility would be a greater bonding of hydrogen between the hydrophilic material and radical OH of O_3, contributing to greater density. The same study also shows that the divergence of stainless components (Ni and Fe) causes alterations in the D value due to the possibility of destroying the O_3 gas. Even though differences in relation to the type of stainless surface were not ob-

served, it may be that differences depend on the polishing procedures used during cleaning.

Only one study reported the results concerning concentration of residues on material and in the environment (E1). In the first case, it required cleaning the product after the process and in the second, it resulted in strong odor and irritation to eye mucosa. The process, however, occurred with a high concentration of O_3 (20,000-30,000 ppm) in experimental equipment and the study does not mention whether aeration was applied after sterilization. Such an issue was not addressed among those studies that mentioned aeration. Therefore, compatible residual concentration levels both for products and environment remain unknown in this review.

The capacity of existing equipment (up to 125 liters) still does not accommodate the large quantity and variety of products to compete with the equipment already available in terms of cost-effectiveness. The relationships of time, humidity and concentration also vary among studies, which prevents reaching a conclusion as to what would be optimal parameters.

Finally, the small number of studies identified, only five, the period when these experiments were performed (from the 1990s on) and the participation of various fields of knowledge denote that the application of O_3 as sterilizing agent for products used in health care is a new proposition still seldom addressed in scientific literature. The variety of scope and products tests, as well as the diversity of experiments, implies that research on O_3 as sterilizing agent is still incipient.

CONCLUSION

Given the urgent need for new processing methods and the continuous development of new technology added to the large diversity of shapes and raw materials, the O_3 gas is, according to the analyses, a promising method. Nonetheless, further research of an experimental nature is required to gather evidence concerning its possibilities and limitations.

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