HIGH-LEVEL DISINFECTANTS ALTERNATIVE TO GLUTARALDEHYDE FOR PROCESSING FLEXIBLE ENDOSCOPES

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ABSTRACT: Flexible endoscopes are fundamental in various medical specialities; in general they are heat-sensitive, semi-critical, and subject to high level disinfection. Glutaraldehyde is largely used for this purpose, due to its high compatibility and low-cost. However, its tolerance of mycobacteria and occupational toxicity lead to pressure being applied for the adoption of alternative germicides. A systematic review was undertaken aiming to seek evidence regarding the effectiveness, toxicity and potential harm caused to the endoscopes by those germicides which are alternative to glutaraldehyde and which are available on the market in Brazil. A total of 822 publications was identified in 13 electronic databases, between 2008 and 2013. Of these, 23 studies were selected, considering the best quality of evidence available. The publications point to the superiority of peracetic acid and of orthophthaldehyde regarding efficacy in high level disinfection. Only orthophthaldehyde presented an adverse event clearly related to its use. There is insufficient evidence to assert that any of these germicides has greater potential for harm to the equipment.
DESCRIPTORS: Disinfection; Endoscopes; Glutaraldehyde; Toxicity.

DESINFETANTES DE ALTO NÍVEL ALTERNATIVOS AO GLUTARALDEÍDO PARA PROCESSAMENTO DE ENDOSCÓPIOS FLEXÍVEIS

RESUMO: Endoscópios flexíveis são fundamentais em diversas especialidades médicas; em geral são termossensíveis, semicríticos e submetidos à desinfecção de alto nível. O glutaraldeído é largamente utilizado para este fim, devido à alta compatibilidade e baixo custo, porém, a tolerância de micobactérias e a toxicidade ocupacional pressionam por adoção de germicidas alternativos. Foi realizada revisão sistemática com objetivo de buscar evidências sobre a efetividade, toxicidade e potenciais danos causados aos endoscópios pelos germicidas, alternativos ao glutaraldeído, disponíveis no mercado brasileiro. Foram identificadas, em 13 bases eletrônicas, 822 publications, entre 2008 e 2013. Destas, foram selecionados 23 estudos, considerando a melhor qualidade de evidência disponível. As publications apontaram para a superioridade do ácido peracético e do ortoftalaldeído quanto à eficácia na desinfecção de alto nível. Somente o ortoftalaldeído apresentou evento adverso claramente relacionado à sua utilização. Não há evidências suficientes para afirmar que algum destes germicidas possui maior potencial de danos aos equipamentos.
DESCRITORES: Desinfecção; Endoscópios; Glutaraldeído; Toxicidade.

DESINFECTANTES DE ALTO NIVEL ALTERNATIVOS AL GLUTARALDEHÍDO PARA PROCESAMIENTO DE ENDOSCOPIOS FLEXIBLES

RESUMEN: Fundamentales en diversas especialidades médicas, los endoscopios flexibles son, normalmente, termosensibles, semicríticos y sometidos a la desinfección de alto nivel. El glutaraldehído es muy utilizado para esa finalidad, en razón de la gran compatibilidad y bajo custo, pero la tolerancia de microbacterias y el hecho de ser o no tóxico de modo ocupacional presionan por la adopción de germicidas alternativos. Fue realizada revisión sistemática con el objetivo de buscar evidencias sobre la efectividad, toxicidad y potenciales daños causados a los endoscopios por los germicidas alternativos al glutaraldehído, disponibles en el mercado brasileño. Fueron identificadas, en 13 bases electrónicas, 822 publicaciones, entre 2008 y 2013. De estas, fueron seleccionados 23 estudios, considerando la mejor cualidad de evidencia disponible. Las publicaciones apuntaron para la superioridad del ácido peracético y del ortoftalaldehído cuanto a la eficacia en la desinfección de alto nivel. Solamente el ortoftalaldehído presentó evento adverso claramente relacionado a su utilización. No hay evidencias suficientes para afirmar que algun de estes germicidas presenta mayor potencial de daños a los equipos.
DESCRIPTORES: Desinfección; Endoscopios; Glutaraldehído; Toxicidad.

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INTRODUCTION

The benefits of using flexible endoscopes for preventing, diagnosing and treating many illnesses are beyond question, and their use is well-established in various medical specialities[1]. This equipment is heat-sensitive, complex, with long and narrow lumens, valves, and intricate commands – which need a rigorous process of cleaning and disinfection, upon each use, in order to avoid the transmission of various infections(1-2). Endoscopes may be classified as critical or semi-critical, according to Spauding's definition which takes into account the level of colonization of the organs where the procedure shall be undertaken[2]. The endoscopes used in the upper or lower digestive tract, and the bronchoscopes, enter the human body through a natural, richly-colonized orifice, and are therefore considered semi-critical equipment. The cystoscopes, although considered semi-critical, must preferentially be subjected to sterilization, due to their use in various surgical procedures. The endoscopes, arthroscopes and rigid optics used in operations are classified as critical, and must mandatorily be sterilized[2].

The semi-critical endoscopes (gastroduodenoscopes, colonoscopes, bronchoscopes, nasofiberscopes, and cystoscopes), due to being used with great frequency and in outpatient procedures of short duration, constitute a challenge for adequate disinfection processes, and are the present study's target. The incidence of infection associated with endoscopies, supposedly, is low, at around one in every 1.8 million procedures. However, outbreaks of infections related to endoscopic procedures are highlighted in the literature, demonstrating that the principal causes are failures in the cleaning and disinfection process[1-3]. This processing, in Brazil, must follow the good practices for Central Sterile Supply Departments and for Endoscopy Services, set out by Collegiate Directorate Resolutions n. 15/2012 and n. 6/2013 of the Brazilian Health Surveillance Agency[4-5].

After use, the semi-critical endoscopes must be subjected to thorough cleaning and High Level Disinfection (HLD) which eliminates all the vegetative micro-organisms (virus, fungi, bacteria and mycobacteria), also having partial action on spores[2]. HLD can be undertaken by manual or automatized methods and meets the requirements established under specific Brazilian regulation[6], which regulates chemical products with antimicrobial action used in critical and semi-critical materials. The disinfectants' level of action, required in this resolution, is proven regarding S*taphylococcus aureus, Salmonella choleraesuis, Escherichia coli, Pseudomona aeruginosa, Trichophyton mentagrophytes, Candida albicans, Mycobacterium smegmatis*, *Mycobacterium bovis* (BCG), *Mycobacterium massiliense* INCQS 00594, *Bacillus subtilis and Clostridium sporogenes*[6].

Although indispensable for disinfection, the germicides have frequently been associated with damage to the endoscopes, such as corrosion, impairment of the fixation of the lenses, softening of the endoscope's external covering tube and incrustation of dirt in the lumens[1-2]. Due to the fact that this equipment is delicate and expensive, there is reluctance to adopt new germicides, especially when there is no express authorization from the manufacturer, which could lead to the cancellation of the guarantee for new endoscopes. The majority of manufacturers recommend only the use of glutaraldehyde; others authorize the use of peracetic acid, although of specific formulation and brands. The following are HLD germicides approved for use in Brazil:

Glutaraldehyde (GLU) is a saturated dialdehyde, slightly acid, volatile and with a pungent odor; it acts through the alkylation of the micro-organisms' sulfhydril, hydroxyl, carboxyl and amines, altering their DNA, RNA and protein synthesis. The sporicidal action occurs through the hardening of the external layers. This remains the disinfectant used most worldwide, by the manual and automatized method, at concentrations varying from 2% to 3.4%. Due to the adverse events observed in patients and professionals, norms were published(4,7-8) with various requirements: handling of GLU in a separate and well-ventilated area, the use of personal protective equipment and collective protective equipment, environmental monitoring and periodical medical evaluation of the professionals. There are reports of cases of intrinsically tolerant micro-organisms, specifically, rapid growing mycobacterium[1-2]. Between 2006 and 2008, in Brazil, an outbreak of post-operative infections occurred, caused by rapid growing mycobacterium, with over 2000 cases notified[9]; the outbreak was strongly associated with video surgery procedures, in which the instruments received HLD with GLU. GLU's lack of effectiveness in relation to the mycobacterias was confirmed by studies of the strains which cause infections(10-11). In order to contain the outbreak, measures were applied by the Brazilian National Agency for Health Surveillance, prohibiting liquid chemical sterilization ("soaking") and increasing the requirements for registering disinfectants and sterilizing agents[6,12-13].

Orthophthaldehyde (OPA) is a soluble and stable aldehyde with a blue coloring, pH of 7.5, sensitive to ultraviolet light and to oxidation by the air; its mechanism of action is similar to that of GLU, although with low sporicidal action, which occurs through blocking germination. This aldehyde can be used manually or automatically, in concentrations of 0.55%; in spite of being less volatile than GLU, it also needs to be handled in an appropriately-ventilated area using personal protective equipment[1-2].

Peracetic Acid (PA) is commercially available in aqueous formulations or as a powder, for manual or automatized use, with rapid action on vegetative micro-organisms. The concentration in which it is used and the pH of the solution are formula-dependent; this disinfectant acts through denaturation of proteins, an increase in the permeability of the cell membrane through rupturing the sulfydryl radicals (-Sh) and sulphur bonds (S-S), oxidising the essential microbial enzymes[1-2]. In Brazil, the use of PA as a disinfectant for endoscopes is relatively recent.

Electrolyzed Acid Water (EAW) is created by equipment which undertake electrolysis of sodium chloride(1,2); it operates with a pH ≥2.7, with a potential oxide-reduction 1000 mV and the formation of free chlorine at a concentration of 10±2 ppm. This product acts through the synergistic action of the pH, the potential for oxide-reduction and oxidation of the hypochlorous acid which inhibits the micro-organisms' metabolism[1-2]. In Brazil, the equipment available is of Japanese origin, and is called Clean Top®[14].

Table 1 presents a summarized form of the advantages and disadvantages of the high level disinfectants.

In the light of the above, the study's objective was a systematic review of the literature, for the analysis of high level disinfectants which are alternatives to GLU, in relation to the effectiveness, the toxicity to patients and health professionals, and potential damage to the endoscopes.

Table 1 - Advantages, disadvantages, and toxicity of the high level disinfectants. Campinas-SP-Brazil, 2013

Product	Advantages	Disadvantages	Toxicity
GLU	- Low cost - excellent compatibility with all the materials - Good stability (14 to 28 days)	- Low sporicidal and mycobactericidal activity at 25°C - Fixes organic material, favoring the formation of biofilm - Requires there to be periodic evaluation of the lung function of the professionals who handle the solution - Requires a minimum time of 20 minutes for disinfection - Volatile	- Irritant for the nose, throat, eyes and skin - Promotes sensitization - Can cause colitis in patients
OPA	- Excellent compatibility - Good stability (7 to 14 days) - Disinfection time from 12 minutes	- Low and slow action on spores - Volatile, but much less so than GLU - Fixes organic material, but much less than GLU - Neutralization of this product is recommended prior to disposal	- Irritant for eyes and respiratory tract - Little data on events related to long exposure times - Anaphylaxis with repeated cystoscopy in cancer patients
PA	- Disinfection time from 10 minutes - Stability is formula-dependent, varying from 1 to 30 days - Atoxic to the environment - Does not fix organic material	- High cost - Odor of vinegar - Variable compatibility, may be corrosive for some alloys and metals. - Can coagulate proteins, depending on the pH	- Depending on the formulation, especially on the pH, can be irritating for the eyes and respiratory tract
EAW	- Disinfection time from 7 minutes - Is not toxic for the professional - Low cost of the process - Wide spectrum of action	- Can be inactivated in the presence of organic material - Can coagulate proteins, depending on the pH - the equipment only processes gastrointestinal endoscopes	- No reports

Key: GLU- Glutaraldehyde; OPA- Orthophthaldehyde; PA- Peracetic Acid; EAW- Electrolyzed Acid Water

METHOD

The PICO methodology was adopted for elaborating the research question: the health problem to which it applies (P = semi-critical flexible endoscopes – gastrointestinal, respiratory and cystoscopes), the technology or intervention to be evaluated (I= PA, OPA and EAW for manual or automatized use), the alternative technologies for comparison (C= GLU) and the health results or outcomes of interest (O= effectiveness in HLD, toxicity and harm to the equipment)(15). The question was defined as "What are the effectiveness, the toxicity and the potential harm to the endoscopes of the high level disinfectants which are alternatives for glutaraldehyde?"

The inclusion criteria for the studies were: 1. Best evidence possible in the literature, considering the outcomes established, considering the level of scientific evidence of the studies according to the Oxford Centre for Evidence Based Medicine(15); 2. Publications since 2008, as two important guidelines were adopted as a starting point, published in that year regarding the processing of endoscopes(1-2). The terms used for the searches are presented in Table 2, through which 822 publications were identified, published up to June 2013. The evaluation of each study was discussed by the authors and by an independent reviewer.

Table 2 - Search strategy and keywords. Campinas-SP-Brazil, 2013

Source	**Keywords**
PUBMED	(disinfection[Title/Abstract]) AND (endoscopy[Title/Abstract]) AND ("2008"[Date - Publication] : "2012"[Date - Publication])
EMBASE	'glutaraldehyde'/exp AND 'endoscopy'/exp AND 'disinfection'/exp; 'peracetic acid'/exp AND 'endoscopy'/exp AND 'disinfection'/exp; 'phthalaldehyde'/exp AND 'endoscopy'/exp AND 'disinfection'/exp; superoxidized water; 'endoscopy'/exp AND 'disinfection'/exp AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py)
COCHRANE LIBRARY	Disinfection and endoscopy
BANDOLIER	Disinfection
CRD	(disinfection) AND (endoscopy) FROM 2008 TO 2012
SUMSEARCH	disinfection AND endoscopy
LILACS	Disinfection and endoscopy
HTAI	Disinfection and endoscopy
PORTAL EVIDÊNCIA BIREME	Disinfection
BDENF	Disinfection and endoscopy
ADVANCED GOOGLE	All in title: glutaraldehyde endoscopy since 2008; all in title: Ortho-phthalaldehyde disinfection since 2008; all in title: peraceticacid disinfection since 2008; all in title: superoxidized water disinfection since 2008; all in title: Electrolyzed Acid Water disinfection since 2008.
BDTD	Title “infecção" #year defended::>2008; title:"endoscopia" #year defended::>2008; title:"glutaraldeído" #year defended::>2008; title:"ácido peracético" #year defended::>2008; title:"água ácida" #year defended::>2008

RESULTS

Figure 1 presents the different stages adopted for selecting the studies. The reasons for the exclusion of the majority of the publications were: in the opinion of specialists, the text did not address the outcomes of interest, and/or had important methodological bias. At the end of the selection, 23 publications were included: 1 systematic review; 2 guidelines; 1 evaluation of health technology; 9 experimental studies; 3 descriptive studies, and, finally, 7 case reports referent to the toxicity of the germicides. The publications originated from 12 countries, with the most frequent being Brazil and the United States of America, with six studies each.

The period from 2008 to 2010 concentrated 74% of the publications. Regarding the outcomes of interest, 14 studies addressed the effectiveness of the HLD, nine also analyzed the toxicity of the germicides, and only four referred to aspects referent to damage to the equipment.

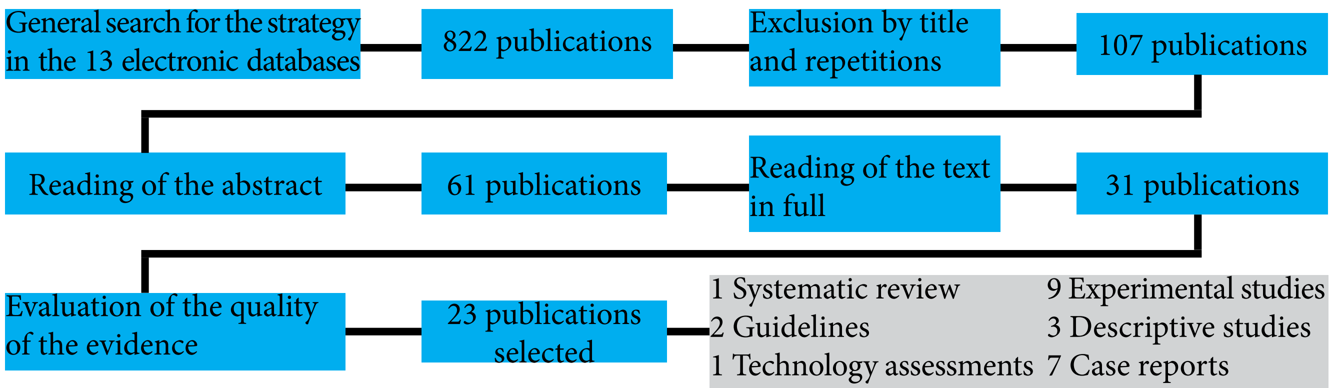

Figure 1- Summary of the stages of selection of the studies. Campinas, SP, Brazil, 2013

DISCUSSION

In relation to the effectiveness of the HLD, there is consensus in the literature regarding the gastrointestinal endoscopes being semi-critical; however, questions remain in relation to the need for sterilization of bronchoscopes and cystoscopes[16].

Three studies analyzed the disinfectants' action in relation to biofilms. One of these indicates that PA has a lower ability to fix protein residues and biofilm, in relation to GLU and EAW[17]. Another publication[18] analyzed the removal of biofilm, exopolysaccharides and bacterias in sample bodies which simulated the channels of flexible endoscopes after the use of various disinfectants. The most efficient was automatized GLU (95.24%), in spite of its known action in the fixing of organic material: this was explained as being due to the double cleaning undertaken by the equipment. PA by manual method presented the worst results (23.81%). If one considers the absence of all residues, PA by the automatized method obtained the best results (66.67%), and EAW, the worst (0%)[18]. The third study only evaluated PA, with satisfactory results regarding the micro-organisms tested, including in biofilm[19].

One systematic review[20] drew attention to the inefficacy of all the high level disinfectants used in Brazil for micro-organisms of the subclass *Coccidia*, this being the principal representative of the genus *Cryptosporidium*, which can cause enteric infection in immuno-compromised patients. In spite of this impacting on the processing of colonoscopes, the authors assert that there remain no recommendations for changing current practices, due to lack of evidence of their impact on the occurrence of infections related to colonoscopy.

Another challenging micro-organism is *Micobacterium massiliense* INCQS 549, a rapid growing mycobacterium, shown to be tolerant to GLU in high concentrations and over a long exposure time[21-22]. Considering PA and OPA, this mycobacteria presented susceptibility in the concentration and exposure time used in care practice[23]. These findings led to the establishment of new legislation for approval, registration and use of disinfectants[4,6,9,12-13,24].

The use of endoscope-disinfecting equipment using EAW remains incipient in Brazil. Of the studies selected, one demonstrates favorable results of its germicidal action regarding various clinical strains and ATCC (American Type Culture Collection), including bacterias and fungi, in a laboratory environment and materials. However, mycobacterias were not tested, and HLD in endoscopes was not evaluated[25]. Another publication which analyzed the action of different disinfectants regarding the biofilm in lumens, simulating the channels of an endoscope, had the worst results in the trials with EAW[17].

Descriptive studies still point to the frequent use of GLU, although alternative germicides have already been adopted in a significant portion of the services(26-27). The use of automatic processes, with different germicides, is addressed in various publications, demonstrating a tendency for the abandonment of manual processing[18,26-30]. However, even using appropriate disinfectants, processors which are not maintained, with flaws in performance, or a poorly-trained team, can cause contamination of the endoscope, cases of infection, and other adverse events[29-33].

In relation to toxicity, the studies reinforce the care steps necessary so as to minimize the occupational risks in handling disinfectants[31,34]. Two studies address adverse events in patients who received procedures with material disinfected by GLU: six cases of post-colonoscopy rectocolitis, related to failure in the rinsing system of the re-processor[29], and two serious cases of lesions in the pharynx after transesophageal echocardiogram, using a catheter impregnated with GLU residues[35].

The literature contraindicates the use of OPA in cystoscopes, due to cases of anaphylaxis in cancer patients who received repeated cystoscopies[31,36-39]. One of the studies stated that it did not evidence any sign of toxicity among the professionals, but notes that the process was mechanized, which minimizes the occupational risks[28].

Two studies report cases of colitis related to the use of PA in the HLD of the colonoscopes; one due to shortcomings in manual rinsing(33), the other due to an error in the programming of the re-processor[30]. The studies did not report cases of occupational toxicity. Only one publication addressed adverse events related to EAW: two cases of colitis, in the endoscopy service of a Brazilian University hospital[40].

Four studies addressed damage to the endoscopes, potentially related to the germicides[27,34,41-42]. The guideline of the American Society for Gastrointestinal Endoscopy confirms that the durability of this equipment remains little known, there being a shortage of public data regarding problems in the functionality, or harm in the process of disinfection, after a certain number of years or of procedures[34]. One interesting report addresses the identification of Pseudomonas aeruginosa, of the same pattern of antibiogram, in the tracheal secretions of various critically-ill patients who underwent bronchoscopy. The investigation of the outbreak concluded that it was related to the use of a specific bronchoscope which had damage in the internal channels and in the structure[42], leading to dirt remaining present, the formation of biofilm, and impedance of the germicidal action.

The literature emphasizes the high compatibility of GLU, but draws attention to its action in the fixing of organic material, which can lead to the obstruction of the channels, should efficient cleaning not be undertaken[17]. In one descriptive study of the HLD practices, in a region of Italy, 67% of the services still used GLU and 77% confirmed that they believed that the disinfectant solution could harm the endoscopes[27]. One descriptive study undertaken to evaluate the length of use of fiberscopes, subject to automatized disinfection by OPA, monitored the occurrence of damage in the equipment and concluded that, the slimmer the fiber, the higher the chance of damage, and that handling by a trained team is fundamental for keeping the equipment in good condition. In the sample, there was no harm related directly to the disinfectant solution[41].

No studies were identified evaluating harm related to PA or EAW.

CONCLUSIONS

The principal limitation of the present review is the shortage of studies with a high level of evidence regarding the high-level disinfectants considering the outcomes analyzed, demonstrating the need for the undertaking of further studies with high methodological rigor for appropriate understanding of the phenomena. Based in the studies analyzed, and in the evidence available, it is ascertained that the PA and OPA solutions are effective in the inactivation of vegetative micro-organisms, whether these are bacteria, fungi, viruses or mycobacteria, so long as the conditions of use established by the manufacturer are followed, good HLD practices are complied with, and the automatic endoscope processors function appropriately. It was evidenced that rapid growth mycobacteria have intrinsic tolerance for GLU. Further studies are necessary on the efficacy of EAW, principally relating to its microbicidal action, and, in particular, the inactivation of *M. massilie*. Micro-organisms of the Coccidia subclass continue to be a challenge, as these are not inactivated by any HLD chemical method available in Brazil.

In relation to occupational toxicity, the use of measures of personal protection and of the environment in the handling of any chemical product is imperative, even though there are no concrete reports of adverse events related to the use of PA and EAW. Of the disinfectants studied, GLU was most cited in relation to toxicity, reinforcing the need for additional measures for control of occupational health should it not be possible to substitute it with less toxic germicides. All the stages of processing must be rigorously followed in order to guarantee patient safety, in particular the effective removal of chemical residues through abundant rinsing. The contraindication of the use of OPA for HLD of cystoscopes remains in place, due to the risk of anaphylactic reactions.

No study was identified reporting damage to endoscopes caused by the solutions of PA, OPA, and EAW, in spite of this being a frequent concern, both on the part of endoscope manufacturers, and the health services. There is insufficient evidence to assert the inferiority of any germicide regarding damage to the equipment, it being noteworthy that, on the subject of PA, there are different formulations available on the market, some explicitly indicated for HLD of endoscopes by the manufacturers, and other formulations lacking this clear indication. Studies emphasize the importance of all professionals who handle the equipment being appropriately trained so as to ensure the preservation of the useful life of this equipment.

Knowledge regarding the germicides allows the appropriate selection for the processing of each type of endoscope, taking into account chemical characteristics, spectrum of action, and restrictions in the choice of disinfectant, as well as the training of the team in good processing practices, the aim being to prevent adverse events related to the endoscopic procedures, occupational toxicity, and damage to the equipment.

DECLARATION OF CONFLICTS OF INTEREST AND ACKNOWLEDGMENTS

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