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REVIEW

Is peracetic acid suitable for the cleaning step of reprocessing flexible endoscopes?

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Abstract

The bioburden (blood, protein, pathogens and biofilm) on flexible endoscopes after use is often high and its removal is essential to allow effective disinfection, especially in the case of peracetic acid-based disinfectants, which are easily inactivated by organic material. Cleaning processes using conventional cleaners remove a variable but often sufficient amount of the bioburden. Some formulations based on peracetic acid are recommended by manufacturers for the cleaning step. We performed a systematic literature search and reviewed the available evidence to clarify the suitability of peracetic acid-based formulations for cleaning flexible endoscopes. A total of 243 studies were evaluated. No studies have yet demonstrated that peracetic acid-based cleaners are as effective as conventional cleaners. Some peracetic acid-based formulations have demonstrated some biofilm-cleaning effects and no biofilm-fixation potential, while others have a limited cleaning effect and a clear biofilm-fixation potential. All published data demonstrated a limited blood cleaning effect and a substantial blood and nerve tissue fixation potential of peracetic acid. No evidence-based guidelines on reprocessing flexible endoscopes currently recommend using cleaners containing peracetic acid, but some guidelines clearly recommend not using them because of their fixation potential. Evidence from some outbreaks, especially those involving highly multidrug-resistant gram-negative pathogens, indicated that disinfection using peracetic acid may be insufficient if the preceding cleaning step is not performed adequately. Based on this review we conclude that peracetic acid-based formulations should not be used for cleaning flexible endoscopes.

Key words: Peracetic acid; Cleaning; Flexible endoscope; Biofilm; Resistance; Bioburden; Blood; Disinfection; Reprocessing

Core tip: Some formulations based on peracetic acid (PAA) are recommended by manufacturers for cleaning flexible endoscopes. We reviewed 243 studies to analyse the evidence for this recommendation. No study demonstrated that PAA-based cleaners were as effective as conventional cleaners, and some PAA-based formulations had clear biofilm-fixation potential. Dried blood and nerve tissue were substantially fixed by PAA. Some outbreaks, especially of highly multidrug-resistant gram-negative pathogens, indicated that insufficient cleaning could not be compensated for by using PAA in the disinfection step. PAA-based formulations should not be used for cleaning flexible endoscopes.

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INTRODUCTION

Flexible endoscopes come into contact with the mucosa

and are considered as semi-critical equipment, associated with a high risk of infection[1,2]. Infections, including those due to multidrug-resistant gram-negative pathogens, quite frequently occur after gastrointestinal endoscopy[3,4]. The most common types of infections are primary sepsis or bacteraemia[3], pneumonia[3] and gastroenteritis[3], some of which may be fatal. Blood-borne infections such as hepatitis B or hepatitis C have also been described[3]. Most infections are attributed to inadequate cleaning or disinfection of the endoscope before its use on the next patient[3,5,6]. The cleaning process or disinfection step is usually described as inadequate if it deviates obviously from national evidence-based guidelines[7,8].

The processing protocols for flexible endoscopes have changed over the last few decades, with an increase in the popularity of automatic processing[9]. This is associated with advantages such as better standardization, better process validation compared with manual processing[10-17], better overall reprocessing results[18,19] and similar costs[20]. The choice of active disinfection ingredients has increased at the same time. Glutaraldehyde continues to be the main active ingredient in the disinfection step for several decades[21] and is often used for automatic processing at high temperatures such as 56 ℃[22]. It is also used for processing other semi-critical medical devices such as flexible cystoscopes[23], rhinoscopy[24] and bronchoscopes[25]. However, some countries now use peracetic acid-based formulations for the disinfection step[10,14,17,26-30]. Some manufacturers of chemical processing products have recently adapted their processing protocols to recommend the use of peracetic acid-based formulations also for the cleaning step. However, the suitability of peracetic acid for cleaning remains controversial. This study aimed to review the scientific literature on all aspects of the use of peracetic acid-based formulations for cleaning flexible endoscopes, and to provide a clinically relevant summary of the possible implications for patient safety.

STUDY SELECTION

A literature review of the National Library of Medicine was performed on August 19, 2013, using various combinations of the following terms: peracetic acid, cleaning, flexible endoscope, endoscope biofilm, resistance, fixation, infection and outbreak. A total of 471 publications were identified and reviewed for their suitability regarding the topic. A total of 172 studies were considered relevant and evaluated in detail. A further 71 studies not identified by the literature search were also evaluated, *e.g.*, guidelines, reports on side effects, additionally referenced studies or reviews (Figure 1).

STANDARD PROTOCOL FOR PROCESSING FLEXIBLE ENDOSCOPES

Flexible endoscopes are usually processed *via* several steps (Table 1). The cleaning step itself comprises three steps[31]. Pre-cleaning is usually done immediately after use of the endoscope, *e.g.*, with detergent-soaked gauze and rinsing of all channels with the cleaning agents. Pre-cleaning is a standard procedure and may be omitted only under certain conditions[32]. Secondly, brush-cleaning involves cleaning all accessible channels with a brush suited to each channel, and is followed by chemical cleaning, which involves filling all the channels with the cleaning agent for a few minutes, followed by thorough rinsing. The subsequent disinfection step varies in duration, depending on the chemical formulation used and the required spectrum of antimicrobial activity; if virucidal or mycobactericidal activity is required, the duration may be longer. Finally, the endoscope is rinsed once more and dried[33]. Double cleaning is recommended in some countries, such as France, mainly because of the risk of prion diseases[34,35].

The cleaning step itself is considered to be difficult in flexible endoscopes because of the long, narrow lumens and multiple valves[36]. In addition, endoscope channels should be freely accessible, because limited access is associated with significantly poorer cleaning results (approximately 3%)[37]. Manual cleaning is considered less effective than automatic cleaning[38].

IMPORTANCE OF THE CLEANING STEP

There are two major reasons for performing effective cleaning before the disinfection step. First, organic and inorganic materials left on the inner and outer surfaces interfere with the efficacy of the disinfectants[39,40], given that blocked channels may remain undisinfected[41]; only a clean endoscope with clean channels can be disinfected effectively[34]. Second, cleaning of flexible endoscopes aims to reduce the bioburden as much as possible[41]. It is generally acknowledged that the cleaning, rather than the disinfection or sterilization procedure, controls the success of the endoscope[42,43] or angioscopy reprocessing procedure[44] although cleaning alone does not reduce contamination to a safe level[45].

Inadequate cleaning may reduce the efficacy of the disinfection step[46,47] finally leading to contaminated flexible endoscopes after processing, mainly with gram-negative bacteria[48]. Chemical disinfectants work by direct contact between the disinfectant and the microbe, which may be prevented by residual organic material, resulting in incomplete microbial killing[49,50]. Inadequate cleaning was regarded as a main reason in various outbreaks of nosocomial infections associated with bronchoscopy or endoscopic retrograde cholangiopancreatography (ERCP)[51-53]. The importance of optimal cleaning of flexible endoscopes for the overall reprocessing results is acknowledged as a significant issue by physicians and gastroenterology nurses[54].

CLEANING AGENTS

The cleaning agent is usually a detergent without any biocidal ingredient[35]. Some cleaning agents are enzymatic,

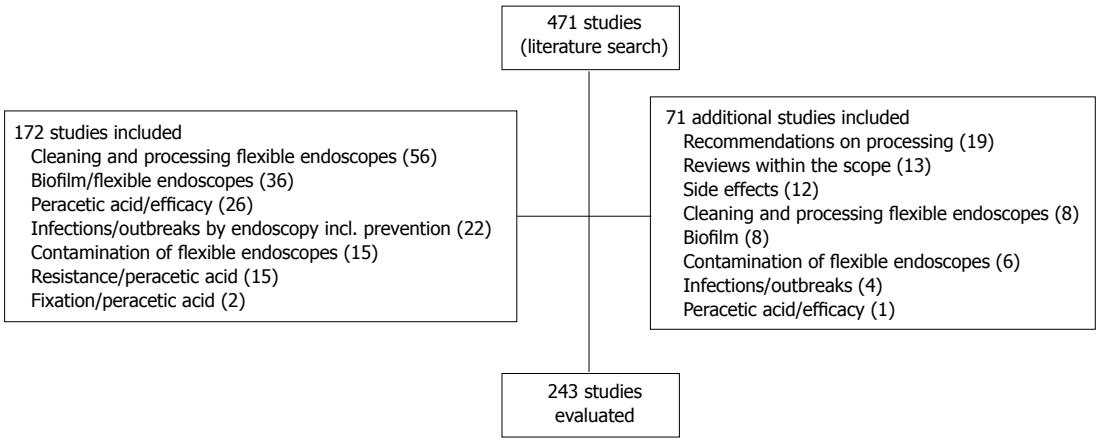

Figure 1 Flow diagram on the study selection process.

Table 1 Typical sequence of steps for manual and automatic reprocessing of flexible endoscopes including the typical duration of the various cleaning steps

Manual processing	Automatic processing
Pre-cleaning the outer surface with a detergent-soaked single-use gauze and rinsing all channels with the cleaning agent, usually for 2 min	
Brush-cleaning all accessible channels with a suitable brush, usually for 3 min	
	Rinsing
Chemical cleaning; filling all channels with the cleaning agent, allowing the cleaning agents to persist inside the channel for approximately 5 min	
Rinsing, usually for 1 min	
Disinfection	
Final rinsing	
Drying	

others are non-enzymatic[55,56]. The cleaning agent should be compatible with the disinfectant agent. The entire process may then achieve a 9 $\log_{10}$ reduction of microorganisms in a tube simulating an endoscope channel[57]. Other processes using different types of cleaning or disinfection agents have revealed lower overall reductions, *e.g.*, a 7 $\log_{10}$ reduction[58]. Lack of use of a detergent in the cleaning step in an automatic processor did not result in any viral blood-borne infections such as hepatitis B or C in 72 patients[59], indicating that the type of cleaning agent is less important in terms of the overall cleaning result for some enveloped blood-borne viruses.

CHEMICAL CHARACTERIZATION OF PERACETIC ACID

Peracetic acid is an oxygen-releasing compound and has been known as a biocidal agent for decades[60-62]. Its current use is mainly for disinfection, *e.g.*, of flexible endoscopes or surfaces[63], sometimes in combination with 1% hydrogen peroxide[64]. In automatic processing of flexible endoscopes, it is used at concentrations of 0.2%[65], 0.35%[66] or even 1%[45], while in manual procedures it may be used at 0.2%[67]. It degrades rapidly to acetic acid and oxygen[68], and its stability is poor compared with glutaraldehyde[69], but may be prolonged by adding stabilizing agents[68]. In common with all oxygen-releasing compounds, it is inactivated by organic materials such as blood[68,70], serum[71,72], albumin[73] or a combination of organic loads[74]. It may be corrosive for a number of materials such as steel or rubber, whereas glass and some plastics are unaffected[68].

FORMULATIONS BASED ON PERACETIC ACID

Various peracetic-acid-based products for processing flexible endoscopes are available in a number of countries; some are powders, and others are liquids used as a one- or two-component system. A number of products available for manual processing are known to the authors and include: Acecide (Saraya Co. Ltd., Osaka, Japan), Gigasept PAA concentrate (Schülke and Mayr, Norderstedt, Germany), neodisher endo DIS active (Chemische Fabrik Dr. Weigert GmbH and Co. KG, Hamburg, Germany), NU Cidex (ASP, Wokingham, United Kingdom), PeraSafe (Antec International Ltd., Sudbury, United Kingdom), Scotalin (KRD, Busan, South Korea), and Sekusept aktiv (Ecolab Inc., St. Paul, MN, United States). Available products for automatic processing include: neodisher Septo PAC (Chemische Fabrik Dr. Weigert GmbH and Co. KG, Hamburg, Germany), Olympus EndoDis (Olympus Europe Holding GmbH, Hamburg, Germany), or Rapicide PA (Medivators Inc. Minneapolis, MN, United States). All these products are described as suitable for the disinfection of flexible endoscopes, but some of them are also recommended by the manufacturer for the cleaning step (Gigasept PAA concentrate, neodisher endo DIS active, and Sekusept aktiv).

PATHOGENS

Pathogens on flexible endoscopes after use

The total contamination of flexible endoscopes with pathogens is usually highest in colonoscopes, followed by gastroscopes and bronchoscopes[75]. The microbial load

after patient examination was found to be between > 10^3 and 10^{10} colony-forming units (CFU) per milliliter[48,76], with highest numbers in the suction channel[77-79]. The contamination consisted mainly of gram-negative bacteria (56%) such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Escherichia coli*, followed by gram-positive bacteria (27%) such as *Staphylococcus aureus*, coagulase-negative *Staphylococcus* and *Micrococcus luteus,* and yeasts (17%) such as *Candida albicans* and *Candida tropicalis*[48]. The air and water channels may, however, also be contaminated[80]. If biopsy suction channels are not adequately cleaned, remaining pathogens may contaminate single-use sterile biopsy forceps during passage[81,82].

Infected patients leave their infectious flora on the endoscope. Hepatitis B virus DNA, hepatitis C virus RNA, human immunodeficiency virus DNA and *H. pylori* have been found after use of endoscopes in infected patients[83-86], especially in the biopsy suction channel[87], and even after cleaning[88]. It is estimated that, on average, 4 in every 1000 endoscopies result in transmission of *H. pylori*[89].

Pathogens on flexible endoscopes after cleaning

The cleaning step can reduce the bioburden by 4.7 $\log_{10}$ CFU (gastroscopes) and 6.2 $\log_{10}$ CFU (colonoscopes)[76,90]. Automatic cleaning and manual cleaning resulted in a similar reduction in microbial load (4.32 and 4.24, respectively), when measured with *E. faecalis* and *P. aeruginosa*[33]. *M. chelonae* may be reduced by 4 $\log_{10}$-steps by standardized manual cleaning[91]. Automatic cleaning processes may achieve a $\log_{10}$-reduction of 7.0-8.4, depending on the type of washer disinfectant and cleaning agent[92].

In contaminated test tubes the cleaning step during automatic processing of flexible endoscopes shows variable results, depending on the type of process and the cleaning agent[58]. Some cleaning processes using a detergent were significantly less effective (0.3 $\log_{10}$-steps) than water alone (1.1-2.6 $\log_{10}$-steps), indicating that the entire cleaning process needs to be evaluated critically[55,56]. In contrast, other cleaning processes were significantly more effective (4.1 $\log_{10}$-steps)[56].

HCV is usually completely removed from the biopsy suction channel by the cleaning step alone, as demonstrated in 19 upper gastrointestinal endoscopic procedures in patients with chronic replicative hepatitis C[85]. This finding is supported by *in vitro* data using contaminated high-titre HCV-positive plasma for experimental contamination of flexible endoscopes[93], and by evaluation of flexible endoscopes used in patients with hepatitis C[94]. HIV was a also reduced by at least 99.93% using a detergent cleaning step alone[95].

Overall cleaning effectively reduces or eliminates many pathogens by at least 4 log as recommended[77], but substantial levels of viable bacteria may remain[78]. This suggests that the risk of transmission of nosocomial pathogens cannot be eliminated by cleaning alone[96]. Poor mechanical cleaning may be indicated by a high titre of microorganisms in a surveillance culture[97].

Effect of peracetic acid on pathogens

Antimicrobial activity: Peracetic acid is very reactive and has strong antimicrobial activity. Depending on its concentration and pH value[98], it is effective against bacteria including *H. pylori*, fungi, mycobacteria, viruses including hepatitis B virus, and bacterial spores[35,66,68,99-112], though for specific isolates, such as *Mycobacterium gordonae*, the exposure time may have to be prolonged to 20 min to achieve the required efficacy[67]. However, despite its broad spectrum of antimicrobial activity it is not suitable for sterilizing surgical instruments[113]. In combination with copper, peracetic acid is also considered to be suitable for prion decontamination[114]. The optimal pH value for its antimicrobial activity is between 2.5 and 4[68]. It is also assumed that exposure of gram-positive species such as *Bacillus subtilis* to chlorine dioxide enhances a stable cross-resistance to other oxidizing agents, such as peracetic acid[74], as confirmed by Bridier *et al*[115]. The efficacies of different formulations differ remarkably compared with solutions of the active ingredient alone[116].

Cellular changes to sublethal concentrations: Bacterial resistance to biocides is apparently increasing, although peracetic acid has not been implicated in the selection and persistence of bacterial strains with low-level antibiotic resistance[117]. Exposure of nosocomial pathogens to peracetic acid at a sublethal concentration (*e.g.*, 1 mmol/L) has been reported to induce a cellular response in *S. aureus*. This response includes the induction of many virulence-factor genes upon exposure, suggesting stimulation of pathogenesis in response to peracetic acid[118]. Other effects included significant alterations in the regulation of membrane-transport genes, selective induction of DNA-repair and -replication genes, and differential repression of primary metabolism-related genes between the two growth states[118]. Similar reactions were observed after exposure of *P. aeruginosa* to a sublethal concentration (*e.g.*, 1 mmol/L) of peracetic acid: many genes associated with cellular protective processes were induced, while transcription of genes involved in primary metabolic pathways was repressed, and that of genes encoding membrane proteins and small molecule transporters was altered[119]. In terms of *E. coli* O157:H7, a sublethal concentration of peracetic acid (0.1%) induced a substantial increase in peroxidative tolerance[120]. Finally, a strain of *Salmonella typhimurium* exposed to a sublethal concentration of peracetic acid (*e.g.*, 15 mg/L) showed modified physiological characteristics: the cells remained viable but were unable to be cultured, but retained their virulence, as shown by their adhesive and invasive capacities[121]. A higher concentration of peracetic acid (*e.g.*, 20 mg/L) resulted in bacterial death. This study indicated that a negative culture result from an endoscope does not exclude the presence of pathogens on the endoscope, and transmission may occur if the bacterial cells modify their physiological characteristics, *e.g.*, by exposure to sub-

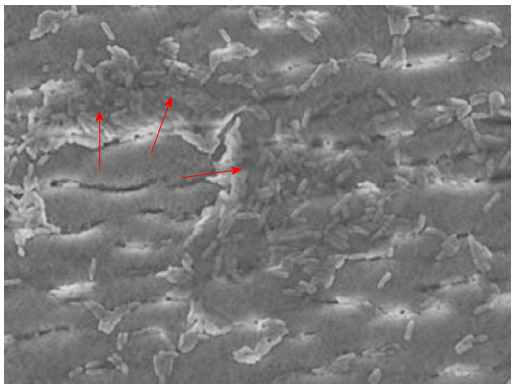

Figure 2 Residual biofilm after exposure to 0.09%-0.15% peracetic acid, as shown by Balsamo *et al*[141]. Reproduced by kind permission of the publisher.

lethal concentrations of peracetic acid.

BIOFILM

General background

Biofilms are communities of cells that are attached to an abiotic or living surface embedded in an extracellular polymeric substance[122,123]. They are preferentially formed in wet environments (*e.g.*, insufficient drying of endoscopes before storage[124,125]), can form under different flow conditions[126,127] and can be potential sources of contamination and infection[128]. Virtually all bacterial species can form biofilm including clinically-relevant ones such as *P. aeruginosa*, *S. aureus*, *E. coli* and *Clostridium difficile*[123,129,130]. Under natural environmental conditions, biofilms are likely to be composed of a mixture of different species[131,132]. In the laboratory, they can be grown on various materials and devices, including polystyrene microtitre plates[133-136], haemolysis glass tubes[137,138], stainless steel coupons[134,139] and also in Teflon tubes[140-143], similar to endoscope channels.

Resistance of biofilm bacteria

One feature of many biofilm bacteria is their resistance to some antibiotics and disinfectants ([144-147] and reviewed in[148,149]). Artificial *P. aeruginosa* biofilms resisted treatment with various biocidal agents including peracetic acid, compared with their planktonic counterparts[150-152]. Biofilms composed of *E. coli*[152,153], *S. aureus*[152,154,155], *Mycobacterium fortuitum*[156] or *Listeria monocytogenes*[157] also resisted treatment with diverse biocides compared with planktonic cells. Bacteria in mature (old) biofilms were more resistant to killing than those in young biofilms[153,158,159]. An older biofilm of *P. aeruginosa* required up to 20-fold higher concentrations of peracetic acid (0.2%) to be eradicated, compared with their planktonic counterparts (0.01%)[151]. Similar results were found with an *E. coli* biofilm and peracetic acid/H_2O_2[153]. The resistance of biofilms can often further increase when the communities are composed of more than one bacterial species[134,136,160-163] which may include resistance against 0.35% peracetic acid, which is a concentration used in many formulations[133]. Especially "build-up" biofilms mimicking repeated endoscope reprocessing cycles exhibited a significantly higher survival rate than 'traditional' biofilms[158]. The mechanisms underlying disinfectant-resistant phenotypes appear to be multifactorial[133,148,151,153,164].

Biofilm on flexible endoscopes

Direct evidence for extensive biofilm contamination was provided in 1 of 13 investigated biopsy suction channels and 5 of 12 air/water channels of reprocessed endoscopes[165]. Some reports showed persistent levels of bacteria in endoscope channels, despite reprocessing according to published guidelines, providing indirect evidence for contamination by biofilms[166-168]. Residual biofilm can be seen in Figure 2. In one case, a colonoscope was contaminated with a total of 195 bacteria despite six rounds of reprocessing[168]. Treatment with a cleaning agent that had previously been shown to remove biofilms from endoscope tubes[142] was capable of eradicating the microbes almost completely, indicating that the presence of biofilm was the main reason for ongoing bacterial contamination[168]. Biofilms were also found in washer disinfectors resulting in contamination of automatically-processed endoscopes, *e.g.*, with *Mycobacterium chelonae*[169,170], *Methylobacterium mesophilicum*[170] or *P. aeruginosa*[171], some giving rise to nosocomial infections[171]. Biofilm formation and fixation should therefore also be avoided in washer disinfectors[172]. If biofilms are not thoroughly removed from endoscope channels by cleaning, subsequent disinfection might fail, enabling microorganisms to persist. Further, efficient interchange of plasmids might occur in biofilms, including those coding for antibiotic resistance such as cefotaxime- or aminoglycoside-resistance[173-176].

Biofilm on flexible endoscopes after cleaning

Shear stress was found to remove some biofilms, though 24% and 47% of the biofilm masses, respectively, remained attached[177]. Brushing a silicone tube 10 times with a sterile brush was found to completely remove a multispecies biofilm that had developed over a period of 50 d[178].

Commercial detergents show variable results on biofilm removal[179]. A non-enzymatic detergent yielded a significantly higher $\log_{10}$-reduction (4.13 to 4.17 $\log_{10}$-reduction) of residual wall *E. coli* biofilm bacteria than the enzymatic detergents (0.74 to 0.88 $\log_{10}$-reduction), whilst contact time (3, 5 or 7 min) had no significant impact[180]. Similar results on different cleaners were reported by Fang *et al*[181] and Vickery *et al*[182]. Quantification of endotoxin levels also revealed better results for a non-enzymatic cleaner in terms of biofilm reduction[183]. A non-enzymatic cleaner continued to remove more biofilm with an increasing number of wash/contamination cycles: by the 20th cycle, 90% of the tubing was biofilm-free[184].

New cleaning formulations based on phosphates, hydrates, minerals and surfactants were developed several

years ago[142]. These formulations effectively removed multispecies biofilms from Teflon tubes, prevented the growth of new biofilms in endoscopes, and established biofilms were completely removed from endoscopes by sequential washing with an enzymatic solution and a bleach-enriched version of the new cleaning formulations[142]. Three repeats of a reprocessing of more than 1 h using sequential application of these cleaning components almost completely removed biofilms from flexible endoscopes that had been used in patients, and were persistently contaminated with bacteria despite six rounds of reprocessing[168]. The practicality of this procedure, however, remains doubtful.

Effect of peracetic acid on biofilm

Treatments with aldehyde, peracetic acid plus detergent, or chlorine failed to disturb or remove biofilm, despite a significant log reduction in biofilm bacteria[178]. Biofilm in a water line in a dental unit with permanent water contact was effectively removed by a peracetic acid flush (0.26%)[185], but this has no correlate in endoscope processing. *P. aeruginosa* biofilms remained in an endoscope prototype in 76.2% of tested tube segments after cleaning followed by manual peracetic acid (0.09%-0.15%) processing and in 23.8% after cleaning followed by automatic peracetic acid processing[141]. The same processes with glutaraldehyde (2%) revealed lower rates of 71.4% after manual processing and 4.8% after automatic processing[141]. Protein in a *P. aeruginosa* biofilm could be removed by peracetic acid by 41%. The removal is much lower from mature biofilms or biofilms subjected to repeated peracetic acid treatments, which may modify biofilm structure[143]. At the same time, the biofilm was partially fixed and accumulated after exposure to two peracetic acid-based formulations[143]. Fixation rates varied between formulations within the same chemical group[143]. Four peracetic acid-based products were reported, two of which fixed artificial biofilms quite strongly, while the other two containing additional quaternary ammonium compounds showed no biofilm fixation[138]. An *E. coli* biofilm exposed to three different peracetic acid-based formulations (one with peracetic acid, one with additional non-ionic surfactant, and one with additional cationic surfactant) was partly removed by two formulations, and not fixed by any of the three formulations[137].

Finally, sublethal concentrations of chlorine dioxide, an active compound used for disinfection of endoscopes, *may accelerate* formation of *B. subtilis or P. aeruginosa biofilms* compared with biofilms grown in the absence of chlorine dioxide[186]. A similar effect can be expected with other oxygen-releasing compounds.

BLOOD

Blood on flexible endoscopes after use

Contamination of flexible endoscopes with blood is to be expected, *e.g.*, after biopsy or in the case of variceal gastrointestinal bleeding. It is also common in other types of endoscopic procedures[187]. After different types of endoscopic procedures, suction channels contain haemoglobin at a concentration of 85 μg/cm^2[78]. Residual blood may contain blood-borne viral pathogens[83,84,87,88] and may impair the efficacy of the subsequent disinfection step[44,68,70,188].

Blood on flexible endoscopes after cleaning

Detergent-based formulations are capable to remove between 88% and 95% of dried blood while peracetic acid-based formulations only removed 8%-59% depending on the type of formulation[183,189]. These results indicate that dried blood is not removed as easily by peracetic acid-based formulations compared with detergent-based formulations.

Effect of peracetic acid on blood

At the same time, however, the rate of fixation of blood exposed to the same peracetic acid-based formulations was between 19% and 78%[189], indicating that the remaining blood is fixed and cannot be easily removed. A similar effect can be seen on clinically used endoscopes containing organic contamination fixed by glutaraldehyde disinfectant solution: 20 cleaning cycles using a buffered peracetic acid procedure removed 30%-50% of the contamination[190]. These data highlight the need to avoid contact between organic contaminant and agents with fixation properties, because subsequent removal may be difficult.

OTHER ORGANIC CONTAMINATION

Organic contamination on flexible endoscopes after use

Suction channels may contain proteins at a concentration of 115 μg/cm^2 after endoscopic procedures[78].

Organic contamination on flexible endoscopes after cleaning

Organic contamination may remain after cleaning. It was reported that 95 out of 504 samples obtained before disinfection and tested for adenosine triphosphate were above the benchmark values (200 relative light units [RLUs])[191], indicating inadequate cleaning[192]. Levels may be as high as 10417 RLUs on the exterior endoscope surface, or 30281 RLUs on the biopsy suction channel rinsates[193].

Haemoglobin and protein may also remain after cleaning. A channel is considered clean if the haemoglobin level is < 2.2 μg/cm^2 and the protein level is < 6.4 μg/cm^2[194]. If all these parameters are fulfilled, the ATP level will be < 200 RLUs[191] which can be considered a validated benchmark from patient endoscopes[195].

Overall, most of the organic contamination is usually removed below benchmark by detergent-based cleaning procedures, although exceptions may occur[196].

Effect of peracetic acid on organic contamination

Peracetic acid used for high-level disinfection of duo-

Table 2 Outbreaks and pseudo-outbreaks reported in connection with biofilm or peracetic acid-based processing of flexible endoscopes

Number/type of infection(s)	Pathogen(s)	Type of endoscopic procedure	Reason for outbreak / pseudo-outbreak	Peracetic acid-based formulations were used for	Ref.
None (pseudo-outbreak)	*Pseudomonas aeruginosa*	Gastroscopy, bronchoscopy	Suboptimal duration of glutaraldehyde application during disinfection; "resistance" to glutaraldehyde may have been enhanced by manual cleaning with peracetic acid-based disinfectant[214]	Cleaning step	[202]
2: infection (not further specified) 3: colonization	OXA-48 *Klebsiella pneumoniae*	Bronchoscopy	A problem with the washer disinfector or the cleaning procedure was assumed as the reason	Cleaning step and disinfection step (Gastmeier P, personal communication)	[203]
4: pneumonia (3 cases); colonization (1 case)	MDR *Pseudomonas aeruginosa*	Gastroscopy	Insufficient initial cleaning, shortening of the immersion time and brushing time, insufficient channel flushing, and inadequate drying prior to storage	Disinfection step	[124]
4: bacteraemia, biliary tract infection, respiratory tract infection 9: colonisation	KPC-2 *Klebsiella pneumoniae*	Duodenoscopy	Contaminated duodenoscope; reason for outbreak: inadequate cleaning	Disinfection step	[204]
8: bloodstream infection 4: biliary tract infection 4: colonization	ESBL *Klebsiella pneumoniae* (CTX-M-15)	ERCP	Insufficient manual cleaning, insufficient drying after processing	Disinfection step	[125]
3: sepsis	*Pseudomonas aeruginosa*	ERCP	Presence of biofilm on undamaged channels	Disinfection step (Kovaleva J; personal communication)	[205]
5: infection (not further specified) 9: colonization	OXA-48 *Klebsiella pneumoniae*	Duodenoscopy	One endoscope had probably a defect resulting in insufficient disinfection	Disinfection step (Gastmeier P, personal communication)	[203]
18: pulmonary infection (4 cases, one of them died); colonization (14 cases)	Imipenem-resistant *Pseudomonas aeruginosa*	Bronchoscopy	Incorrect connectors joining the bronchoscope suction channel to the STERIS SYSTEM 1 processor	"Automatic processing"	[206]
2: bacteremia and biliary tract infection 4: colonization	KPC-2 *Klebsiella pneumoniae*	Gastroscopy	Delayed pre-wash resulting in drying of the gastroscope; short drying period after the peracetic acid treatment resulting in incomplete drying	"Wash"	[207]

ERCP: Endoscopic retrograde cholangiopancreatography.

denoscopes yielded significantly lower levels of protein (4.2 μg/mL *vs* 10.1 μg/mL), carbohydrate (18.5 μg/mL *vs* 111.1 μg/mL) and endotoxin (2.8 EU/mL *vs* 44.5 EU/mL) in the biopsy suction channels compared with processes using glutaraldehyde[197]. Despite the differences between the two active agents used only for the disinfection step, the authors concluded there may be a cumulative build-up of organic material components on the inner lumen of the biopsy suction channels of endoscopic retrograde cholangiopancreatography scopes in use[197]. An outbreak of eight fatal cases of *Serratia odorifera* septicemia was caused by contaminated parenteral nutrition fluid due to inadequate cleaning of the surfaces prior to the use of peracetic acid[198]. Dialyzers cleaned with peracetic acid showed significantly lower clearance of larger dextrans as a result of the presence of residual proteins on or within the membrane[199]. Similar findings were reported with a product containing hydrogen peroxide and peroxyacetic acid, compared with one containing sodium hypochlorite[200].

Special case: effect of peracetic acid on nerve tissue

Exposure of brain homogenate to peracetic acid (1500 ppm for 20 min) is associated with a very high protein fixation rate of 96%, which is much higher than with exposure to glutaraldehyde (19%)[201]. Mice inoculated with variant Creutzfeld-Jacob disease (vCJD)-infective brain homogenate previously exposed to peracetic acid survived on average 291 d, which was significantly shorter than mice inoculated with negative control homogenate (> 450 d). Mice inoculated with vCJD-infective brain homogenate previously exposed to glutaraldehyde (2% for 20 min) survived longer compared with the peracetic acid group (mean: 324 d), demonstrating a clinical correlate of the almost complete fixation of brain homogenate protein by peracetic acid[201].

OUTBREAKS AND PSEUDO-OUTBREAKS

Outbreaks and pseudo-outbreaks connected with peracetic acid-based processing of flexible endoscopes are summarized in Table 2. In some outbreaks peracetic acid was used for the cleaning step[202], the cleaning and disinfection step[203], the disinfection step[124,125,203-205] or generally for processing/washing[206,207]. The reasons for the infections were insufficient (initial) cleanin[124,125,202-204], inadequate drying prior to storage[124,125,207], shortening of the immersion time and brushing time[124], insufficient channel flushing[124], a problem with the washer disinfec-

Table 3 Adverse effects after processing with peracetic acid after endoscopy

Number of cases	Type of reaction	Possible explanation	Ref.
10	Colitis	Unclear, reprocessing with PAA, but afterwards channels were flushed with hydrogen peroxide	[210]
1	Colitis	PAA residues in the biopsy suction channel	[215]
2	Colitis	Defect of automatic rinsing of a channel	[216]
1	Colitis	Channel not flushed	[217]
1	Colitis	Inadequate rinsing of a channel	[212]
No number provided	Pseudolipomatosis	Air channels not rinsed	[218]
4	Colitis	Programming error in the automatic disinfection device, related to the air/water channels	[219]
12	Colonic mucosal pseudolipomatosis	Rinsing was not done as recommended	[220]

Table 4 Overview of evidence-based guidelines for processing flexible endoscopes, focusing on the use of peracetic acid during the cleaning step

Institution	Guidelines	Year	Use of peracetic acid for cleaning
AORN	Recommended practices for cleaning and processing endoscopes and endoscope accessories[221,222]	2012	No recommendation
APIC	APIC guidelines for infection prevention and control in flexible endoscopy. Association for Professionals in Infection Control[223]	2000	No recommendation
APSIC	The ASEAN Guidelines for disinfection and sterilization of instruments in health care facilities[224]	2012	No recommendation
ASGE	Multisociety guidelines on reprocessing flexible gastrointestinal endoscopes: 2011[225,226]	2011	No recommendation
BC Ministry of Health	Best Practice Guidelines For Cleaning, Disinfection and Sterilization of Critical and Semi-critical Medical Devices[227]	2011	No recommendation
BSG	BSG Guidelines for Decontamination of Equipment for Gastrointestinal Endoscopy[228]	2008	No recommendation
CDC	Guidelines for Disinfection and Sterilization in Healthcare Facilities, 2008[229]	2008	No recommendation
ESGE/ESGENA	ESGE/ESGENA Technical Note on Cleaning and Disinfection[230][1]	2003	**Recommended**
ESGE/ESGENA	ESGE-ESGENA guideline: Cleaning and disinfection in gastrointestinal endoscopy, update 2008[231]	2008	No recommendation
HPS	Endoscope Reprocessing: Guidance on the Requirements for Decontamination Equipment, Facilities and Management[232]	2007	No recommendation
JGETS	Guidelines for cleaning and disinfecting endoscopes - Second edition[233]	2004	No recommendation
Public Health Agency of Canada	Infection Prevention and Control Guideline for Flexible Gastrointestinal Endoscopy and Flexible Bronchoscopy[234]	2010	No recommendation
RKI	Hygiene requirements for reprocessing of medical devices[235][2]	2001	No recommendation
RKI	Hygiene requirements for reprocessing of medical devices[236]	2012	**Not recommended**
SGNA	Standards of Infection Control in Reprocessing of Flexible Gastrointestinal Endoscopes[237]	2013	No recommendation
WGO/OMED	WGO/OMED Practice Guideline Endoscope Disinfection[238]	2005	**Recommended**
WGO/WEO	Endoscope disinfection - a resource-sensitive approach[239]	2011	No recommendation

[1]These guidelines were updated in 2008 by guidelines[231]; [2]These guidelines were updated in 2012 by guidelines[236]. AORN: Association of periOperative Registered Nurses; APIC: Association for Professionals in Infection Control and Epidemiology; APSIC: Asia Pacific Society of Infection Control; ASGE: American Society for Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology; CDC: Centers for Disease Control and Prevention; ESGE: European Society of Gastrointestinal Endoscopy; ESGENA: European Society of Gastroenterology and Endoscopy Nurses and Associates; HPS: Health Protection Scotland; JGETS: Japanese Gastroenterological Endoscopy Technicians Society; OMED: Organisation Mondiale d'Endoscopie Digestive/World Organization for Digestive Endoscopy; RKI: Robert Koch Institute; SGNA: Society of Gastroenterology Nurses and Associates, Inc; WEO: World Endoscopy Organization (former OMED); WGO: World Gastroenterology Organisation.

tor[203], presence of biofilm on undamaged channels[205], an endoscope defect[203], delayed pre-wash resulting in drying of the gastroscope[207], and incorrect connectors joining the bronchoscope suction channel to the STERIS SYSTEM 1 processor[206]. Strict adherence to infection control guidelines for reprocessing endoscopes is therefore the key element for prevention of endoscope-associated outbreaks[203].

CLINICAL SIDE EFFECTS OF PERACETIC ACID

The potential health risks associated with all high-level disinfectants are considered to be serious, though little is known about the risks to humans, especially employees, from glutaraldehyde alternatives[208,209]. Gutterman *et al*[209] identified only eight studies "which reported numerous adverse outcomes to healthcare personnel associated with endoscope reprocessing", including one case report with asthma for workers using a peracetic acid and hydrogen peroxide based product. The most commonly-reported side effect of peracetic acid in patients is a form of colitis, previously known as pseudolipomatosis[210], which is commonly induced by hydrogen peroxide and peracetic acid but occasionally also by glutaraldehyde[211]. The colitis is often self-limiting but sometimes requires medical treatment. The frequency of colitis caused by peracetic

Table 5 Effects and possible outcomes of peracetic acid use for cleaning flexible endoscopes

Characteristic, reason for cleaning step	Effect of peracetic acid	Possible outcome, compared with classical cleaning
Removal of biofilm	Variable[1]	Insufficient removal of biofilm
Fixation of biofilm	Possible[1]	Fixation of biofilm to variable degrees
Removal of dried blood	Partial removal[1]	Insufficient removal of dried blood
Fixation of dried blood	Very likely	Fixation of dried blood to variable degrees
Fixation of brain tissue	Very likely	Strong fixation of nerve tissue, including prions
Adaptation of microorganisms surviving the cleaning step	Likely, especially in gram-negative bacteria	Insufficient efficacy of disinfection step, persistence of pathogens, beginning of biofilm formation
Cross-resistance to other biocidal compounds as a result of exposure to sublethal peracetic acid concentrations	Possible	Insufficient efficacy of disinfection step, persistence of pathogens, beginning of biofilm formation

[1]Depending on the formulation.

acid might be underestimated[212]. An overview of all reported cases is summarized in Table 3.

REVIEW OF NATIONAL AND INTERNATIONAL GUIDELINES

An overview of 17 guidelines from 14 different institutions is given in Table 4. Most institutions make no statement on the suitability of peracetic acid for cleaning flexible endoscopes, but there seems to be a recent trend in a few institutions to either skip their earlier recommendations of peracetic acid (ESGE/ESGNA and WGO/WEO) or to state that it is not suitable for cleaning (RKI).

CONCLUSION

Few national and international guidelines highlight the need for the cleaning of flexible endoscopes to be carried out using formulations without any fixation potential, but use of peracetic acid for cleaning is discouraged. Some peracetic acid-based formulations have some cleaning capacity. However, we found no conclusive evidence to suggest that the cleaning capacity of any peracetic acid-based formulation was as good as that of detergent-based cleaning agents without biocidal agents. Different peracetic acid-based formulations have been shown to enhance surface fixation of dried blood (all tested formulations), biofilm (some tested formulations) and brain tissue (all tested formulations). Fixed blood and biofilm are likely to impair the efficacy of the disinfection step, given that peracetic acid is known to lose its antimicrobial activity in the presence of various types of organic load. Fixed biofilm will reduce the susceptibility of microorganisms present in the biofilm, making it more difficult to achieve the required log-reduction during the disinfection phase. Even if the bacteria within a biofilm are killed by a disinfectant, microorganisms are likely to adhere to any residual biofilm structure within the endoscope more easily during the next endoscopic procedure.

Table 6 Practical tips to ensure optimal cleaning of flexible endoscopes

Clinical practice tip	Major advantage	Ref.
Clean promptly after use	No drying of organic material such as blood	[77,207]
Follow the instructions of the endoscope manufacturer as closely as possible (*e.g.*, type of brush or cleaning adapter)	Optimum cleaning of an entire channel	
Prefer washer disinfectors with a monitoring system indicating channel blockage	A blocked channel cannot be cleaned adequately and is immediately identified; targeted brush cleaning may be necessary	
Do not switch off the monitoring system for detection of blocked channels	Channels may be blocked and inadequately cleaned; personnel may not detect blocked channels with all possible implications for patient safety	
Support by gastroenterologist	It is strongly recommended that the clinician fully understands the cleaning and disinfection steps and does not inhibit his or her staff's ability to perform them correctly	[240]
Allow external audits by local health authorities on the quality of processing including cleaning	Implementation of guidelines may be more successful if the local health authorities visit the endoscopy units and compare current practices with the relevant guidelines. This effect seems to be more easily achieved in in-patient rather than in out-patient endoscopy units	[241-243]

Published research suggests that peracetic acid-based agents are not suitable for use in the cleaning step during the processing of flexible endoscopes (Table 5). However, some practical tips may help to improve the quality of the cleaning step (Table 6). This review highlights that protocols for processing flexible endoscopes should be evidence-based, rather than being based on convenience[213].

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REVIEW

Recent trends in endoscopic management of achalasia

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Abstract

Esophageal achalasia is a chronic and progressive motility disorder characterized by absence of esophageal body peristalsis associated with an impaired relaxation of lower esophageal sphincter (LES) and usually with an elevated LES pressure, leading to an altered passage of bolus through the esophago-gastric junction. A definitive cure for achalasia is currently unavailable. Palliative treatment options provide only food and liquid bolus intake and relief of symptoms. Endoscopic therapy for achalasia aims to disrupt or weaken the lower esophageal sphincter. Intra-sphincteric injection of botulinum toxin is reserved for elderly or severely ill patients. Pneumatic dilation provides superior results than botulinum toxin injection and a similar medium-term efficacy almost comparable to that attained after surgery. Per oral endoscopic myotomy is a promising option for treating achalasia, but it requires increased experience and further objective and long-term follow up. This article will review different endoscopic treatments in achalasia, and summarize the short-term and long-term outcomes.

Key words: Achalasia; Endoscopy; Pneumatic dilation; Botulinum toxin injection; Per oral endoscopic myotomy; High resolution manometry; Dysphagia

Core tip: No definitive treatments of achalasia are currently available. Palliative treatment options aims to relieve symptoms and to help patients for food and liquid intake. Endoscopic approach to achalasia is directed to disrupt or weaken the lower esophageal sphincter. On the other hand, intra-sphincteric injection of botulinum toxin is reserved for elderly or severely ill patients. Pneumatic dilation provides better results than botulinum toxin injection and a clinical benefit comparable to surgery. Per oral endoscopic myotomy is a promising option but it requires increased experience and further objective and long-term follow up.

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INTRODUCTION

The term "achalasia" (from the Greek "alfa" and "chalasis", words for absence of relaxation) was introduced by Lendrum in 1937[1]. Before that and since then, a host of other names have been used, including achalasia cardiae, cardiospasm, and esophageal aperistalsis, reflecting the key physiological abnormalities of the

disease. The incidence of achalasia is expected to be 1 in 100000 persons per year with a prevalence of 10 in 100000. This disorder can appear at any age, with a two peaks incidence at 20-40 and 70-80 years, without gender prevalence[2]. Esophageal achalasia has been credited to a loss of myenteric plexus ganglionic cells in the esophagus, but its cause remains uncertain[3,4]. Achalasia is characterized by the absence of esophageal body peristalsis associated with an impaired relaxation of the lower esophageal sphincter (LES), and usually with an elevated LES pressure[5,6]. Obviously, these features lead to a failure in the passage of bolus through the esophagogastric junction. The predominant symptom in most patients with achalasia is dysphagia, often for both solids and liquids, or "paradoxical" (first for liquids, then for solids) as a distinction from organic dysphagia. Other symptoms often reported are listed as regurgitation, chest pain, heartburn, and weight loss. Patients with achalasia may also present with symptoms such as slow eating or "augmenting pressure" manoeuvres, to allow a bolus passage through gastric cardia; this may hesitate in delaying medical examination, with a progressive dilation of esophageal lumen[7]. Patients who are suspected to be affected by achalasia commonly require endoscopy, barium esophagram and esophageal manometry for diagnosis[8]. Endoscopic evaluation of the esophagus and stomach must rule out a malignancy or a stenosis causing dysphagia. In achalasia patients, it is common to detect a dilation of esophageal lumen, with food deposit and fluid collection; tight LES appears to be tight and passage through the esophago-gastric junction with the endoscope is perceived as a "pop" opening. Nevertheless, a common esophagus appearing at upper endoscopy can be found, because up to 40% of patients with early-stage disease will have an apparent lack of dilated esophagus[9]. On barium esophagram, achalasia is characterized by the presence of a dilated esophagus, absence of peristalsis, and an impaired passage at the esophagogastric junction, associated with symmetric, smooth narrowing of the region ("bird's beak" sign). Accumulation of barium is seen in the body of the esophagus, especially in patients with huge dilation and curvature of the lower esophagus[10]. Although endoscopic examinations and esophagography currently play an important role in the diagnosis, esophageal motility evaluation by means of manometry is considered the "gold standard" test for achalasia. Classically, at standard esophageal manometry, achalasia is diagnosed when esophageal body peristalsis is totally lacking (absence), often associated to a LES resting pressure > 45 mmHg (hypertensive) and a poorly relaxing LES (residual pressure > 8 mmHg)[11]. Recently, high-resolution manometry (HRM) has been introduced as a new technique for the evaluation of esophageal motility disorders. HRM uses 1 cm spaced pressure sensors spanning thorough the whole esophagus, distal pharynx and proximal stomach, enabling the motility to be displayed as concrete colour images. The new Chicago classification has been proposed to classify esophageal motility disorders on HRM. Achalasia is now organized into 3 types (Ⅰ, Ⅱ and Ⅲ) according to the esophageal motor function[12]. In particular, "classic achalasia" (Type I) appears as a peristaltic esophagus with no distal increase in pressure > 30 mmHg; "achalasia with pan-esophageal compression", or type Ⅱ, has to show at least 20% of liquid swallows with a body pressurization > 30 mmHg, and "spastic achalasia" (type Ⅲ) is described when at least 20% of liquid swallows appears to be spastic contractions, associated or not to a pressurization. In this study, the authors showed that achalasia with pan-esophageal compression was associated with a better symptom response and a lower necessity to undergo several treatments than the other 2 types. A definitive cure for achalasia is currently unavailable. Palliative treatment options provide only transit of food and liquid bolus through the gastroesophageal junction, thereby relieving feeding and symptoms. These treatments include drug therapy, endoscopic botulinum toxin injection (BTI), endoscopic pneumatic dilation (PD), per oral endoscopic myotomy (POEM), and surgical extramucosal myotomy, with or without an anterior, posterior or total fundoplication. This article will review different endoscopic treatments in achalasia, and summarize the short-term and long-term outcomes.

ENDOSCOPIC BOTULINUM TOXIN INJECTION

Botulinum toxin can impede the release of acetylcholine from cholinergic neurons. Chemical denervation after an injection of botulinum toxin is intended to lower both basal and residual LES pressure, therefore reducing bolus obstruction[13,14]. Usually, an endoscopic needle is used to inject 20 to 25 units of botulinum toxin into quadrants, at the squamocolumnar junction or up to 1 cm proximally, for a total dose of 80 to 100 units. Recommendations are given to inject the toxin equally in a circumferential manner and at the same level, avoiding submucosal injection or injection outside the esophageal wall. Different authors proposed alternative solutions to improve outcomes, such as injecting by means of endoscopic ultrasound or using different types of botulinum toxin, but these remained only experimental practices[15]. Commonly, 70%-80% of patients referred showed relieved or improved symptoms within 30 d after the procedure.

After BTI, patients occasionally referred transitory non-cardiac chest pain and only those who experienced a beneficial effect of the toxin rarely reported reflux. Severe complications related to BTI are reported only as isolated cases (fatal arrhythmia, gastroparesis and mediastinitis), probably due to technical difficulties during procedures[16]. In an initial study, Pasricha *et al*[17] reported 82% of patients with dysphagia improvement after BTI. Annese *et al*[18] showed 75% of subjects with dysphagia

remission at 2 years follow-up; however some of the patients required at least one repeated BTI. The short-term effectiveness of BTI was also investigated by Neubrand *et al*[19] using esophageal manometry 1 wk after treatment; LES pressure dropped from 62.1 ± 15.2 mmHg to 43.1 ± 12.5 mmHg ($P < 0.01$). However, symptomatic remission induced by BTI usually decreases within one year (40.6% at one year or longer)[20]. Also, the appearance of antibodies against botulinum toxin or development of regional fibrosis can dissipate the effects of successive injections[21]. BTI was found to be effective only in the short-term evaluation, with reduced benefit within 2 years after injection and eventually with none after repeated injections[22,23]. Because of these limitations, BTI is best reserved for patients who are too ill to undergo surgery, such as elderly patients or patients whose disease is complicated by overlapping diseases or those declining surgery or PD[24]. Compared to PD and surgery (myotomy), BTI was clearly inferior at mid and long term efficacy[25]. A recent Cochrane Review evaluated 178 patients from 6 randomized, controlled trials after esophageal dilation *vs* endoscopic botulinum toxin injection. At one year follow up, up to 74% of patients who underwent BTI were found to have failed treatment, compared to 30% of patients who underwent dilation[26]. Also, Campos *et al*[20], performing a systematic review and a meta-analysis on 7855 achalasia patients, found a better symptomatic relief when treated by PD than BTI. A recent review on 5 best evidence papers trials on BTI *vs* surgical myotomy reported that surgery should be the first line treatment due to its superior long-term clinical success rate[27]. BTI has been used as rescue treatment after unsuccessful PD or surgical myotomy[28]. There is an increased risk for perforation during PD[29], or increased difficulty of performing esophagomyotomy after BTI[30].

PNEUMATIC DILATION

Pneumatic dilation (PD) in patients with achalasia aims to forcibly fracture the muscularis propria, decreasing LES pressure and thereby improving bolus transit through cardia. Forceful dilation of the LES dates back to 1674, when Willis used whalebone as a prototypic bougie to accomplish distraction of the muscular fibres in the esophago-gastric junction[31]. Subsequently, dilation has been performed by various techniques. In fact, up to date, there is no well-standardized, unique technique performing PD in achalasia patients, with different technical modifications. Recently, a ⩾ 3 cm polyethylene low-compliance balloon (Rigiflex Achalasia Balloon Dilator, Boston Scientific, Boston, MA, United States) has been most widely used because it is considered the safest and most effective[20], nevertheless other companies produce analogous devices. These polyethylene balloons are more consistent than latex ones, with the advantage that a fixed diameter (usually as 30, 35, 40 mm sizes) can be achieved during inflation. The position

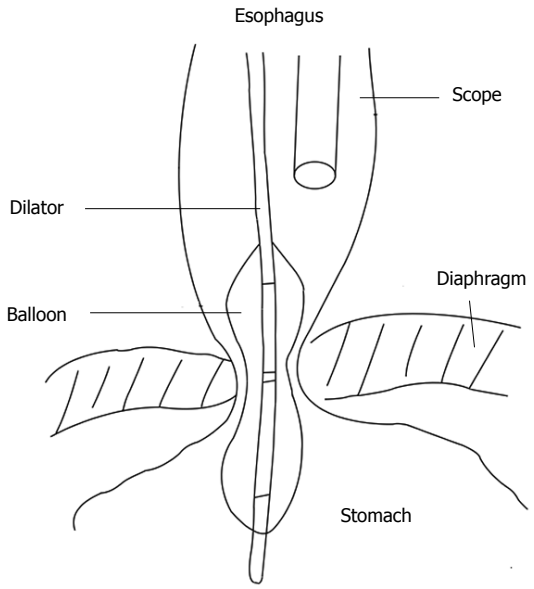

Figure 1 Pneumatic dilation under direct endoscopic guidance (from ref.[32]).

of balloon across the LES is typically performed using a guidewire and fluoroscopy. In recent times, PD has been performed during endoscopic direct imaging rather than fluoroscopy guidance in order to avoid radiation exposure and to obtain a better clinical response and limiting complications (Figure 1). However, even if both fluoroscopically and endoscopically guided PD are safe and effective techniques, the authors were not able to demonstrate differences in outcomes[32]. During endoscopy, a metallic guidewire with a soft distal tip is passed through the LES, then the balloon is put along the wire, until its centre is correctly placed through the esophagogastric junction. After fixing the device by a firm grasp to avoid distal migration during the procedure, the balloon is filled slowly with air until a value of 7 to 10 psi on sphygmomanometry is reached. The aim is to sustain dilation until the LES waist appears closed around the balloon; some prefer a prolonged dilation whereas others deflate the balloon immediately afterwards[33]. Then the balloon device and guidewire are removed. Commonly, blood presence around the balloon cannot be considered a useful marker of successful PD. With the use of a Rigiflex Achalasia Balloon Dilator, the mean time required to reach the required pressure for PD was reported to be 73 s (range, 6-240 s), with a mean dilation pressure of 10.9 psi (range, 7-18)[20]. Usually, an esophageal RX transit with hydro-soluble (gastrografin) contrast agent can be carried out after anesthesia recovery, to verify the presence of lumen perforation and perhaps treatment outcome. There is general agreement that a single dilation, when successful, could be more efficient over time. However, patients typically require serial dilations to remain clinically silent. Success rates of PD are reported up to 84.8% within one month after the procedure, as stated in a systematic review carried out by

Campos *et al*[20] However, success rates declined on longitudinal follow-up; in fact, the success rate was reported to be 73.8% at 6 mo, 68.2% at one year, and 58.4% at 3 years or longer. Also, 25% of patients required a second or a repeated PD. Several studies with a long-term follow-up are currently available. Eckardt *et al*[34] showed with a unique PD a response of 40% at 5-year follow-up, and patients with relieved symptoms at 5 years were more likely to continue in this way, whereas Zerbib *et al*[35] reported an estimated efficacy of 97% and 93% at 5 and 10 years respectively, but frequently with repeated PD. In a study on 209 patients with a mean follow up of 70 mo, a success rate with balloon dilation was observed in 72% of subjects[36]. However, in these studies PD is not routinely repeated, but only performed on demand for still-symptomatic patients; instead, in the study by Hulselmans *et al*[36] patients repeated PD with a bigger balloon only if manometry and barium esophagram did not show optimal treatment outcomes. Long-term efficacy of PD was investigated only in a few studies that have followed-up patients over a decade[37]. The authors concluded that PD, when performed by experienced operators, can achieve good to excellent outcomes (defined as a better swallowing ability and a better quality of life); however, only a few patients can be definitively treated with a first, single dilation, needing repeated dilations at long term follow-up[38]. The most common complication of PD is esophageal perforation, being reported to occur, fortunately, in less than 5% of dilations. Moreover, improvements in balloon materials and other factors have decreased the incidence of perforation to 1.6% on average[20,39]. PD-associated perforation seems to not be related to any well confirmed risk factors and there is no evidence that larger balloons are linked to an increased perforation rate[40]. The PD-linked overall complication rate is estimated to be lower than 10%; these include perforation, transient non-cardiac chest pain, esophagogastric lacerations, hematomas, hemorrhage, fever, and formation of diverticula[41]. Esophageal perforation may be treated with a completion myotomy emergently by a laparotomy, or more recently, performed *via* laparoscopy[42]. Reflux symptoms can be present after PD, reflecting a success in widening the gastroesophageal junction[43]. Several factors are considered responsible for predicting outcomes after PD. Eckardt *et al*[44] showed that, if after PD a manometrical-determined LES pressure of 10 mmHg or less is achieved, this can be the most important predictor of long-term clinical response and that response rates in patients younger than 40 years are relatively lower. Duranceau *et al*[45] reported that grade 4 achalasia patients ("sigmoid esophagus" or "end-stage" disease) generally do not show a good response to PD (or to other treatments). Ghoshal and colleagues instead reported that poor outcomes were associated with sex (male gender) and with a missed drop in LES resting-pressure > 50% after dilation, but they were not related to age, or other factors such as elevated dysphagia score, presence of regurgitation, end stage esophagus, or initial LES resting-pressure[46,47]. Recent use of HRM has suggested, based on Chicago classification, that those with type I and type II (classic and compressive achalasia, respectively) respond much better to PD than those with type III (spastic achalasia)[48]. The role of PD in comparison to surgery is still debated. Both techniques produce an optimal initial resolution of dysphagia; nevertheless surgery is considered to be superior at longer follow up[22,49]. A study by Gockel *et al*[50] showed comparable clinical outcomes with surgical myotomy and PD, but surgery achieved a better LES resting-pressure drop. On the other hand, only a few prospective randomized controlled trials comparing these techniques are available in the literature. There has been a single randomized prospective trial examining outcomes in 81 patients after Heller myotomy plus Dor fundoplication *vs* pneumatic dilation, with a median follow-up of about 5 years[51]. In this trial, investigators found that patients undergoing myotomy resulted in similar relief of dysphagia, but had fewer relapse of symptoms at longer follow-up than those patients undergoing PD (95% success rate *vs* 65%, respectively). However, an important limitation of this study was that dilation was performed with a Mosher bag rather than with a Rigiflex balloon dilator, currently considered the most effective dilator. In a prospective randomized study by Boeckxstaens *et al*[52], PD was compared with surgical therapy (laparoscopic Heller myotomy plus Dor' s fundoplication), using a rigorous design. The study included 201 patients, with a 43 mo mean follow-up; at 12 mo, the two groups showed no significant difference in dysphagia and overall Eckardt score. At 24 mo, the success rate was similar; there was no difference in LES resting-pressure, esophageal transit during RX-barium swallow, or quality of life. However, when a 35-mm balloon was used for dilation in this study, perforation occurred in 4 (31%) of 13 patients. This protocol was abolished during the study. With a balloon 30 mm in diameter, the perforation rate decreased to 4%. In either case, however, PD is associated with a substantial risk of perforation and has not been shown to be clearly superior to surgical therapy in terms of safety. PD can be also considered for a second treatment ("salvage") in patients that had a prior unsuccessful myotomy, but the efficacy rate is reported to be lower when compared to those patients who underwent only dilation[53].

PER ORAL ENDOSCOPIC MYOTOMY

Per oral endoscopic myotomy (POEM), first described by Inoue *et al*[54,55] developed from a technique to access the mediastinum in Natural Orifice Transluminal Endoscopic Surgery (NOTES)[56]. The technique of POEM can be summarized in the following steps: (1) lift of submucosa by injection, and creation of esophageal mucosa tear; (2) tunnellization in the submucosal

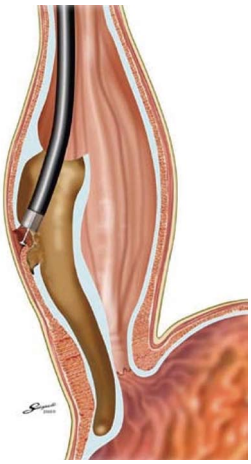

Figure 2 Per Oral Endoscopic Myotomy; creation of submucosal tunnel and inner myotomy (from ref. [55]).

space; (3) identification and separation of esophageal circular muscle; (4) myotomy; and (5) repair of the mucosal tear. A fundamental step of POEM is the creation of a submucosal tunnel with subsequent closure of the mucosal tear entry site away from the myotomy (Figure 2). An endoscopic myotomy of inner circular muscle within this tunnel is then performed, accomplishing a minimal dissection of the LES circular muscle. The myotomy of clasp fibers is performed by grasping the inner muscle layer with a hook and dividing them with an electrocautery-based device. This dissection of muscle is continued distally until it is extended 1-2 cm into the cardia. The overall cut length is approximately 12 cm. The mucosal defect is closed with endoscopic clips. Finally, an easy and smooth passage of an endoscope through the gastroesophageal junction is confirmed at the end of the procedure. This procedure is performed during general anaesthesia with endotracheal intubation. Inoue *et al*[55] initially indicated POEM for the treatment of early-stage achalasia, but recently he described POEM performed in 16 sigmoid achalasia patients, extending the indication to all categories of achalasia, including longstanding disease. Contraindications to endoscopic myotomy include severe pulmonary disease, significant coagulation disorder and prior therapy that compromise esophageal mucosal integrity. Inoue *et al*[57] have treated 43 cases of achalasia, with a maximum follow-up period of 1 year 9 mo. Symptoms of achalasia decreased or disappeared in all patients. The LES pressure decreased significantly after the procedure. No specific complications related to POEM were reported. Although about 10% of patients had gastroesophageal reflux disease after the procedure, symptoms resolved in response to treatment with a proton-pump inhibitor. Actually, there are only series from a few centers[58,59] but literature on POEM is drastically increasing, reflecting the world wide interest in this technique. In follow-up studies, von Renteln *et al*[60] used POEM to treat 16 patients with achalasia and reported similar, favourable results; Li *et al*[61] reported a treatment success (Eckardt score $\leqslant$ 3) in 96% (95 of 99) of patients treated with a full-thickness myotomy and in 95% (115 of 121) of patients treated with circular muscle myotomy. Recently, 70 patients who underwent POEM at 5 centres in Europe and North America, were enrolled in a prospective, international, multicenter study, aiming to determine the outcomes of this technique[62]. At the first follow-up (3 mo) after the procedure, 97% of subjects displayed complete symptom relief (95%CI: 89%-99%); dysphagia and other mean symptoms scores dropped from 7 to 1 ($P < 0.001$) and LES resting-pressures fell from 28 to 9 mmHg ($P < 0.001$). At 6 and 12 mo follow-up visits, symptom relief was found in 89% and 82% of patients, respectively. The authors concluded that POEM, at a 10 mo mean follow-up, can be considered an effective treatment in the management of achalasia. Swanstrom *et al*[63] described 6-mo physiological and symptomatic outcomes in 18 patients after POEM for achalasia. The authors found that all investigated patients displayed remission of dysphagia (dysphagia score $\leqslant$ 1), whereas only 2 patients showed Eckardt scores > 1, related to persistent non cardiac chest pain. During the POEM procedure, 3 intraoperative complications were noted: 2 gastric mucosal tears and 1 esophageal perforation. In all patients, surgeons were able to repair the esophageal and gastric wall endoscopically without any further comorbidity. All patients reported a persisting dysphagia resolution at 11.4 mo mean follow-up. Postoperative LES relaxations and esophageal transit were found to be strongly improved, when investigated by manometry and RX barium esophagogram, respectively. However, the postoperative presence of gastroesophageal reflux was objectivized in 46% of patients. The latter data are in contrast with the low rate (10%) of reflux reported by Inoue[55]. In theory, POEM might not damage anti-reflux barriers such as phrenoesophageal ligamentous attachments and, therefore, may not additionally require an anti-reflux procedure. Gastroesophageal reflux should be prevented to some extent, but objective studies, as previously performed after laparoscopic Heller myotomy plus fundoplication[64,65] are needed. Recently, Verlaan *et al*[66] studied the physiological outcomes of POEM on the esophagogastric junction, reporting 60% rate of reflux esophagitis at endoscopy. Although POEM is expected to become a state-of-the-art technique for minimally invasive surgery in patients with achalasia, it is associated with the risk of serious complications such as mediastinitis and peritonitis caused by perforation of the esophagus or stomach. At present, therefore, it should be performed with caution and only by operators proficient in both esophagoscopic submucosal dissection and open or laparoscopic Heller myotomy. Recent studies compared POEM with laparoscopic Heller myotomy alone[67], or with laparoscopic Heller myotomy plus a partial fundoplication[68], showing similar rates in dysphagia relief. Wider use of POEM would require the results of large,

multicentre clinical trials demonstrating the safety of this procedure. Follow-up studies should also be performed to establish the long-term effectiveness of POEM.

CONCLUSION

As endoscopic treatment for achalasia, PD is superior to BTI. Botulinum toxin injection may be reserved for severly ill patients. It is difficult to make definitive conclusions regarding the comparison between PD and surgery with fundoplication, however Heller mytomy with fundoplication appears to be better especially in young patients. POEM is expected to become a valid substitute for Heller myotomy, but long-term outcomes, the real incidence of "*de novo*" GERD and safety must be confirmed.

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MINIREVIEWS

Laparoscopy for ventriculoperitoneal shunt implantation and revision surgery

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Abstract

Ventriculoperitoneal shunting (VPS) is a widely accepted technique for the treatment of hydrocephalus. The probability of shunt dysfunction is pretty high throughout life. Laparoscopy has become a valuable tool to perform VPS and treat abdominal complications. An electronic literature search was performed to reveal the published data relating laparoscopy and ventriculoperitoneal shunt in Medline, Embase, Scielo and Lilacs databases. The keywords employed were "laparoscopy" OR "laparoscopic surgery" AND "ventriculoperitoneal shunt" OR "shunt" AND "surgery" OR "implantation" OR "revision" OR "complication". No high quality trials were developed comparing conventional laparotomic incision *vs* laparoscopic approach. Both approaches have evolved and currently there are less invasive options for laparotomy, like periumbilical small incisions; and for laparoscopy, like smaller and less incisions. Operating room time, blood loss and hospital stay may be potentially smaller in laparoscopic surgery and complications are probably the same as laparotomy. In revision surgery for abdominal complications after VPS, visualization of whole abdominal cavity is fundamental to address properly the problem and laparoscopic approach is valuable once it is safe, fast and much less invasive than laparotomy. Ventriculoperitoneal shunting is a widely accepted technique for the treatment of hydrocephalus. Laparoscopy assisted shunt surgery in selected cases might be a less invasive and more effective option for intrabdominal manipulation. The laparoscopic approach allows a better catheter positioning, lysis of fibrotic bundles and peritoneal inspection as well, without any additional complication.

Key words: Cerebrospinal fluid shunt; Hydrocephalys; Laparoscopy

Core tip: Review of application of laparoscopy in ventriculoperitoneal surgery.

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INTRODUCTION

Shunt surgery represents a paramount procedure in neurosurgical practice, as the most widely performed central nervous system surgery. The preferred modality is the ventriculoperitoneal shunt (VPS), which connects the lateral ventricles and the peritoneal cavity[1-4].

Up to 80% of shunts implanted for treatment of hydrocephalus may fail at some point during the patient's life, with approximately 30% failing within the first year. Although shunt placement is a common procedure and is considered safe, several complications may occur. Shunt-

related complications, such as obstruction, overdrainage, loculation, and infection, sometimes require challenging surgical approaches associated with increased morbidity[1-6].

Abdominal complications of VPS are not rare, and the common mechanism involves epithelial responses to the presence of the catheter, which cause peritoneal retraction, intra-abdominal cerebrospinal fluid (CSF) collections, and adhesions. These complications usually worsen with multiple peritoneal revisions, sometimes resulting in peritoneal sclerosis that make further shunt implantation infeasible[7].

Within this context, the laparoscopic approach has grown in popularity as an alternative method for shunt implantation and especially for revision surgery after abdominal complications. This paper summarizes current concepts about its application.

RESEARCH

A critical review of the literature was performed after searching the MEDLINE, Embase, SciELO, and LILACS databases for published data on laparoscopy and ventriculoperitoneal shunting. The search query employed was "laparoscopy" OR "laparoscopic surgery" AND "ventriculoperitoneal shunt" OR "shunt" AND "surgery" OR "implantation" OR "revision" OR "complication".

We selected all papers in english, spanish and portuguese. The above search strategy yielded 240 manuscripts. Of these, 110 discussed other uses of laparoscopy not related to ventriculoperitoneal shunting, such as laparoscopy for abdominal and urological surgery. One hundred and thirty papers addressed the topic of interest. As some of these articles presented outdated data or very similar discussions, we selected 30 up-to-date manuscripts discussing different points of view to summarize recent, pertinent information about applications of laparoscopic surgery in ventriculoperitoneal shunting (Figure 1).

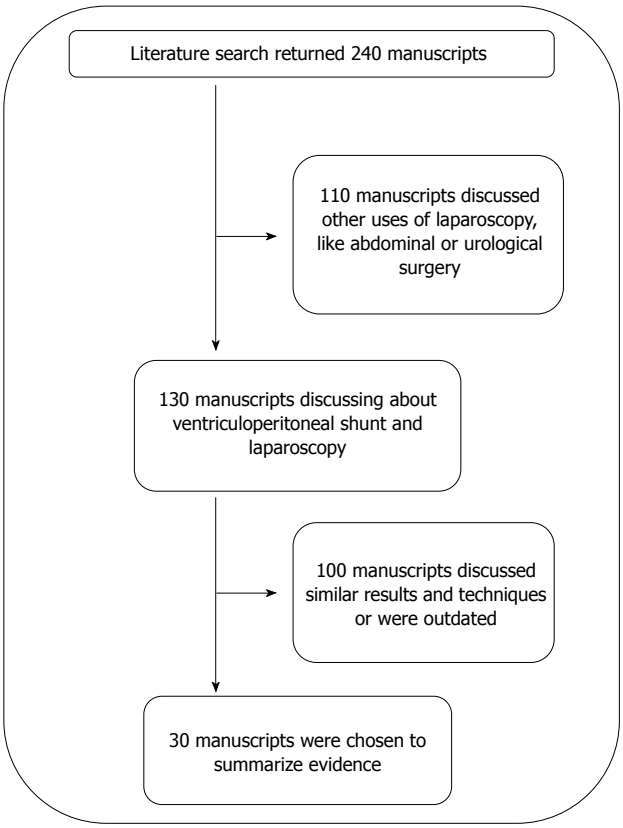

Figure 1 Flowchart of articles evaluated in revision.

LAPAROSCOPY FOR SHUNT IMPLANTATION

Several reports highlight the utility of the laparoscopic approach for abdominal shunt insertion through less invasive incisions[8-10]. No high-quality trials were found comparing conventional laparotomy *vs* laparoscopic approaches. The rationale supporting conventional laparotomy includes factors such as the simple learning curve, as it can be performed by neurosurgeons, and its established success rate. The rationale for laparoscopic approaches includes wide view of catheter implantation, ability to choose the best site for fixation, and confirmation of patency[11-15].

Both approaches have evolved. Currently, less invasive options are available both for laparotomy - such as small periumbilical incisions - and for laparoscopy, such as smaller and fewer incisions using 2-mm trocars[16-20].

Operating room time, blood loss, and hospital stay may be reduced in laparoscopic surgery, and complications are probably the same as with laparotomy[19].

LAPAROSCOPY FOR REVISION SURGERY

In revision surgery for abdominal complications after VPS, the main findings may be abdominal adhesions, peritoneal thickening and retraction, and CSF pseudocysts. Additionally, after complicated VPS, catheter malfunctioning may occur due to migration, occlusion, and presence of foreign bodies[8,21-23].

In such scenarios, visualization of the whole abdominal cavity is essential to addressing the issue properly. The laparoscopic approach is valuable in this setting because it is safe, fast, and much less invasive than laparotomy, and is thus associated with fewer complications[24-27].

DISCUSSION

Ventriculoperitoneal shunting is a widely accepted technique for the treatment of hydrocephalus. The standard procedure to insert the peritoneal catheter requires an abdominal incision, muscle dissection, and opening of the peritoneum. The probability of lifetime shunt dysfunction is quite high. Abdominal complications are major causes of dysfunction. The peritoneal space is forced to accommodate a foreign body (catheter) and receive the flow of approximately 21 mL of CSF per hour, resulting in epithelial responses which may lead to inflammation

and obstruction[1-4].

Several alternative procedures have been reported as temporary or permanent solutions to VPS failure, such as catheter implantation in other distal sites in the cervical, thoracic, and abdominal regions. The ventriculo-omental bursa shunt, with catheter insertion through the foramen of Winslow, has been described, even in cases of peritonitis or peritoneum adhesion. However, all of these options are considered third-line procedures, due to their higher complexity and high complication rates[27].

Laparoscopic-assisted surgery has become an useful option, as it allows abdominal exploration with shorter surgical time and complications. In 1993, Armbruster *et al*[10] and Basauri *et al*[11] described the laparoscopically assisted implantation of ventriculoperitoneal shunts, and in 1995, Kim first described the laparoscopic management of an abdominal complication[11,21].

On the other hand, laparoscopic surgery for other purposes may interfere with VPS function and even cause obstruction. The impaction of soft tissue or air within the distal catheter as a consequence of peritoneal insufflation may cause shunt obstruction[28]. Furthermore, increased abdominal pressure may have a negative effect on intracranial pressure (ICP). Human data on the effects of laparoscopy on ICP are lacking, but ICP increases significantly with abdominal insufflation and correlates with laparoscopic insufflation pressure. Thus, laparoscopy should be performed cautiously in patients with elevated baseline ICP[29].

In conclusion, we believe that laparoscopic-assisted shunt surgery in selected cases might be a less invasive and more effective option for intra-abdominal manipulation. The laparoscopic approach also enables better catheter positioning, lysis of fibrotic bundles, and peritoneal inspection without any additional complications.

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ORIGINAL ARTICLE

Updates on gastric electrical stimulation to treat obesity: Systematic review and future perspectives

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Abstract

AIM: To evaluate the current state-of-the-art of gastric electrical stimulation to treat obesity.

METHODS: Systematic reviews of all studies have been conducted to evaluate the effect of different types of gastric electrical stimulation (GES) on obesity.

RESULTS: Thirty-one studies consisting of a total of 33 different trials were included in the systematic review for data analysis. Weight loss was achieved in most studies, especially during the first 12 mo, but only very few studies had a follow-up period longer than 1 year. Among those that had a longer follow-up period, many were from the Transcend® (Implantable Gastric Stimulation) device group and maintained significant weight loss. Other significant results included changes in appetite/satiety, gastric emptying rate, blood pressure and neurohormone levels or biochemical markers such as ghrelin or HbA1c respectively.

CONCLUSION: GES holds great promises to be an effective obesity treatment. However, stronger evidence is required through more studies with a standardized way of carrying out trials and reporting outcomes, to determine the long-term effect of GES on obesity.

Key words: Gastric electrical stimulation; TANTALUS® system; Transcend® implantable gastric stimulator; Retrograde gastric electrical stimulation; Gastric vagal nerve stimulation; Gastric pacing; EMPOWER trial; Dual-lead implantable gastric electrical stimulation trial; Laparoscopic obesity stimulation survey; Screened health assessment and pacer evaluation

Core tip: Obesity is a major issue in many countries. Current medical treatments do not last long enough and while surgical interventions are more effective, they imply a higher risk of complications. This review contains the most up-to-date information on gastric electrical stimulation, which has shown to be a less invasive and potentially effective treatment option for the treatment of obesity.

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INTRODUCTION

The rate of excess weight and obesity has constantly increased over the past 30 years, and about one third of the world's adult population is overweight[1]. Impressive

excess weight and obesity rates have also been recorded in children and adolescents[2,3]. In Northern America, two thirds of the population is either overweight or obese and in most European countries, the prevalence ranges from 40% to 50%[4]. Projections up to year 2030 indicate that more than 36% of the population in developed countries will be overweight and that more than 22% will be obese[5].

Obesity is a complex multi-factorial, psychoneuroendocrine and metabolic problem, and not simply an imbalance between energy intake and energy expenditure. Obesity is associated with many co-morbidities, including diabetes, hypertension, dyslipidemia, obstructive sleep apnea, weight-related arthropathies, and urinary incontinence[6]. Recent studies also showed that obesity is a major risk factor for cancer[6,7]. Obesity and its co-morbidities lead to an increased use of the health care system and this consequently has a negative economic outcome[8]. Up to 20% of total annual United States healthcare expenditures, around 190 billion dollars, may have been spent on obesity-related medical care in 2005[9,10].

The main therapeutic approaches to obesity are lifestyle correction, pharmacotherapy, surgery and electrical devices[11].

Lifestyle management includes diet and exercise, aiming for more energy expenditure as compared to food intake. However, weight loss maintenance by means of dieting is difficult to manage in the long term. Similarly, Food and Drug Administration (FDA)-approved weight control drugs, such as sibutramine and orlistat, have a very low success rate, and may have considerable side-effects[12].

Surgery seems to be the only effective treatment to achieve sustainable weight loss[13,14] and reversal of obesity-related co-morbidities. Surgical treatment includes three subgroups-restrictive, malabsorptive, and combined restrictive and malabsorptive procedures. Bariatric surgical options can result in up to 80% of long-term excess weight loss (EWL)[15]. However, surgical interventions are invasive and this entails potential postoperative complications[16-19]. Additionally, a very small percentage (less than 1%) of eligible obese patients eventually undergo bariatric surgery[20,21]. This seems to be related to various reasons, including lack of insurance coverage in some countries, as well as psychological factors related to the permanent anatomical changes and potential postoperative complications[20,21].

Less invasive anti-obesity therapies, which are increasingly used, include intragastric balloons (space-occupying devices) and bezoars, which are collections that accumulate, coalesce and are retained in the gastrointestinal tract[22]. These devices are not very well tolerated and long-term results are disappointing. More recently, endoluminal bypassing devices, such as the Endobarrier® or the duodenojejunal bypass liner, seem to be effective in improving glycemia in type 2 diabetes patients by improving insulin sensitivity, demonstrating a crucial role of the duodenum in the genesis of the metabolic syndrome. However, these devices must be anchored endoscopically at the pylorus or at the esophagus with full-thickness fixations, and their presence is often symptomatic, with spastic pain.

The gastric electrical stimulator (GES) has been identified as a potential alternative minimally invasive surgery, based on the growing knowledge on gastrointestinal physiology[23].

The concept of GES to treat obesity was initially proposed in 1995 by Cigaina[15,24,25] who demonstrated the proof of the concept in a series of animal experiments. The exact mechanisms of GES remains largely unknown, but it is thought to impair physiological gastric electrical activity (*i.e.*, slow waves), inducing gastric distension, gastric accommodation reduction, and stomach peristalsis inhibition, leading to delayed gastric emptying and increased satiety[26]. The type of stimulation can be divided into two groups-antegrade and retrograde. The difference between them is the direction of conduction. Antegrade stimulation imposes forward conduction of impulses whereas retrograde stimulation conveys impulses in a backward fashion. GES is also thought to have an effect on neuronal activity in the brain and to affect satiety hormones[26].

Since the discovery of GES, many animal experimental studies have been performed, followed by several clinical trials on human subjects. However, the number of high quality trials is limited and no meta-analysis on GES exists to date. In this systematic review of the literature, we aimed to provide the most up-to-date state-of-the-art on the clinical applications of GES stimulators for obesity.

MATERIALS AND METHODS

The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[27].

Literature search

A broad search was initially performed using the key words "Gastric Electrical Stimulation" and "Obesity" in MEDLINE®/PubMed® and in The Cochrane Library. A more specific search was then performed using the name of each device, as outlined in Table 1. No limit was set at this stage. Duplicate articles were removed and further relevant articles were identified by cross-referencing all searched articles.

Study selection

All published studies investigating the effect of various types of GES on obesity were included. Either an abstract or a full text of each study was manually assessed based on the following exclusion criteria: (1) Language of the article is not English; (2) GES was used for diseases other than obesity (*e.g.*, gastroparesis); (3) Non-gastric stimulation (*i.e.*, stimulation in other areas such as intestine); (4) Animal or experimental study; (5) Primary outcome is not clinical (*i.e.*, no weight, BMI or appetite change measured); and (6) Abstracts without adequate

Table 1 Search terms and results obtained from different databases

Search terms	Database 1 Pubmed	Overlapping Pubmed articles	Total number of articles from Pubmed	Database 2 Cochrane	Database 3 Medline
Gastric electrical stimulation and obesity	145	0	145	5[1]	9[1]
TANTALUS® and obesity	12	7	5	1[1]	6[1]
Enterra® and obesity	6	6	0	0[1]	2[1]
Transcend® and obesity	13	5	8	0[1]	4[1]
Implantable gastric stimulator and obesity	22	12	10	3[1]	2[1]
Retrograde gastric electrical stimulation and obesity	13	3	10	0[1]	2[1]
Gastric pacing and obesity	26	20	6	1[1]	8[1]
Neural gastric electrical stimulation and obesity	6	6	0	0[1]	3[1]
Total number of articles after duplicate removal			184		

[1]Duplicate articles (*i.e.*, these articles are already included in the results of the Pubmed literature search).

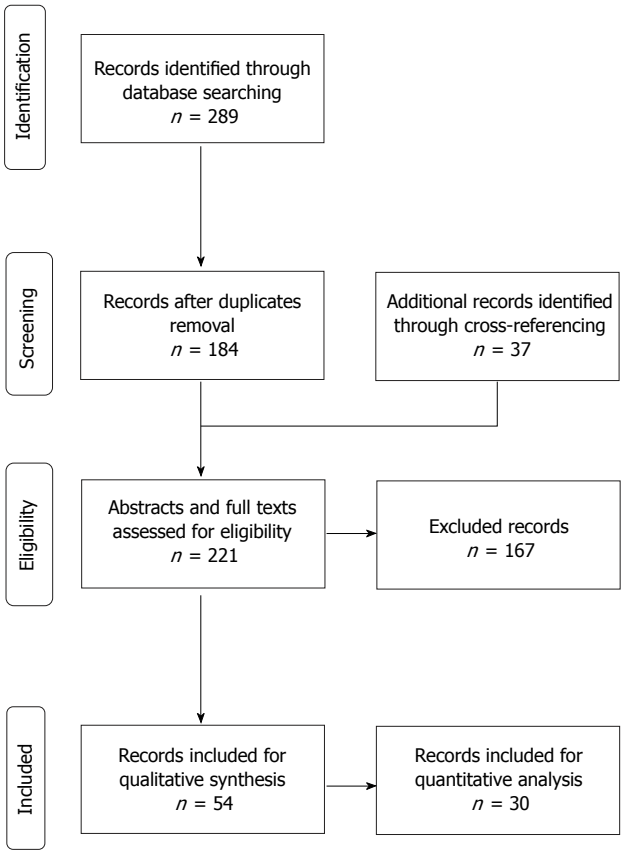

Figure 1 Preferred reporting items for systematic reviews and meta-analysis flow chart.

amount of information on quantitative data. From the studies that remained after the exclusion process, only clinical trials on human subjects were included for data extraction and analysis.

Data extraction

Data were extracted and entered into a pre-designed Excel spreadsheet. The areas of interest were the following: (1) Study designs-sample size, drop-out rate, follow-up period, mean age of participants, baseline weight, BMI, dietary/lifestyle information; (2) GES device parameters-device and electrode implantation sites, type of stimulation, pulse width, amplitude, frequency; and monitoring during and after implantation including any complications due to implantation; (3) Significant outcomes-weight loss, appetite reduction, increased satiety, HbA1c, ghrelin level and gastric emptying rate; and (4) Adverse effects, side-effects or complications at follow-up consultations.

RESULTS

Study selection

The literature database search yielded 289 records, including duplicates. After removing duplicate records (n = 105), 184 articles were collected from various combinations of search terms and databases outlined in Table 1. These records were screened manually to identify further relevant articles and as a result, 37 additional studies were added by cross-referencing. Out of a pool of 221 abstracts and full-text articles, 167 articles were excluded. In a total of 54 articles, 30 clinical trials on human subjects were identified and were included for data extraction. The other 24 studies including reviews, reports, and editorials were excluded from the data analysis but were used for qualitative synthesis, as reported in Figure 1.

General study characteristics

The summaries of all included studies are provided in Tables 2-6. Most studies were non-randomized trials, except 4 studies (including 2 SHAPE trials and 1 U.S. O-01 trial) that were randomized trials. Four Transcend® studies[21,28-30] conducted Baroscreen™ screening, and five Transcend® studies[21,28,31-33] required participants to follow a certain diet and change in behavior. None of the studies assessing other devices required diet or lifestyle changes with the exception of the EMPOWER study[34] for vagal nerve stimulation.

Sample size for most studies was very small. Out of 31 different trials, 24 had about 30 or fewer participants. Five Transcend® studies[20,21,30,35,36] had large participant numbers, but most of them had a drop-out rate of more than 50% by the end of their trials. The studies with low drop-out numbers were the SHAPE trial by Shikora *et al*[21], 2009 (10 drop-outs), and the two TANTALUS® trials[37,38] (0 drop-out in both trials). The EMPOWER study by Sarr *et al*[34] in 2012 had 41 drop-outs but had a large population group of 294 at the beginning of the study,

Table 2 Summary of TANTALUS® trials

Ref.[1]	Sample size (*n*), enrolled/completed	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/ advice given)	Co-morbidities
Lebovitz *et al*[38], 2013	40/40	NR	110.5 ± 3.5/NR	NR	NR/NR	NR
Sanmiguel *et al*[70], 2009	14/11	42	107.3 ± 20.1/39 ± 1	6	N/Y	T2DM
Bohdjalian *et al*[39], 2009	24/21	50.0 ± 1.6	123.7 ± 4.5/41.9 ± 1.0	12	NR/NR	T2DM
Policker *et al*[37], 2009	50/50	NR	NR/NR	6+	NR/NR	T2DM
Bohdjalian *et al*[71], 2009	13/13	53.8 ± 2.6	104.4 ± 4.4/37.2 ± 1.1	3	N/Y	T2DM
Policker *et al*[69], 2008	12/12	50.8 ± 2.2	130 ± 6.5/NR	9	N/Y	T2DM
Sanmiguel *et al*[43], 2007	12/11	39.1 ± 8.9	NR/41.6 ± 3.4	1.5	N/NR	T2DM
Bohdjalian *et al*[72], 2006	12/9	36.1 ± 2.8	128.8 ± 5.2/43.2 ± 2.7	12	N/Y	HTN

[1]All trials were open-label and none were randomized. T2DM: Type 2 diabetes.

Table 3 Implantable gastric stimulator Transcend®: Studies summary

Ref.	Type of research	Sample size, (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/advice given)	Baroscreen®
Korner *et al*[28], 2011	Randomized + D, PC (SHAPE)	13/13	48.8	113.1/40.6	24	Y/Y	Y
Shikora *et al*[21], 2009	Randomized + P, D, M, PC (SHAPE)	190/180	43.9	NR/41	12	Y/Y	Y
Hoeller *et al*[73], 2006	Non-randomized	8/7	48.1	112.5/41.3	23	NR/NR	N
Champion *et al*[29], 2006	Non-randomized + O	24/21	43	92/33	6	Y/Y	Y
Miller *et al*[30], 2006	Non-randomized + P, M (LOSS trial)	91/25	41	116/41	24	N/Y	Y
Shikora *et al*[20], 2005	randomized + D, PC (O-01 trial)	103/34	40	129/46	29	NR/NR	N
Shikora *et al*[20], 2005	Non- randomized + O, M (DIGEST)	30/23	39	NR/42	24	Y/Y	N[1]
Cigaina *et al*[32], 2004	Non- randomized	65/NR	39.4 ± 3.4	132.7 ± 27.3/46.9 ± 7.07	96[2]	Y/Y	NR[1]
Favretti *et al*[74], 2004	Non- randomized	20/20	40	115/40.9	10	N/Y	NR
De Luca *et al*[36], 2004	Non- randomized + P (LOSS trial)	69/20	41	115/41	15	NR/NR	NR
Cigaina *et al*[75], 2003	Non- randomized	11/11	39.4 ± 3.4	121.7 ± 5.1/46.0 ± 2.5	8	N/Y	NR
McCallum *et al*[35], 2002	randomized + D	103/NR	40	NR/46	12	NR/NR	NR
D'Argent *et al*[76], 2002	Non- randomized + P, O	12/NR	40.6	122.2/42.7	9	NR/NR	NR

[1]No Baroscreen® conducted but binge eating assessment questionnaire and a psychological evaluation were carried out; [2]This study had four different cohorts over the 8-yr period, from 1996 to 2004.

Table 4 Retrograde gastric electrical stimulation-studies summary

Ref.[1]	Sample size (enrolled/ completed)	Mean age (yr)	Mean weight, (kg)/mean BMI (kg/m^2)
Zhang *et al*[41], 2013	16/16	39	NR/32.1
Yao *et al*[44], 2005	12/12	29.4 ± 8.6	62.62 ± 8.29/23.2 ± 2.6
Yao *et al*[77], 2005	12/12	29.4 ± 8.6	62.62 ± 8.29/23.18 ± 2.62

[1]All trials were non-randomized; no follow-up length and lifestyle change advice reported.

making it one of the most powerful studies for vagal stimulator and obesity.

There were two articles about the Transcend® Implantable Gastric Stimulator (IGS) (MEDTRONICS, Inc., Minneapolis, MN, United States) based on the same data, but because each article had two different trials, the total number of trials did not change. There was one article from the gastric pacing device group, which included 3 different cohorts at different time periods[33]. As a result, it was counted as 3 different trials.

The full text for one article, "The implantable gastric stimulator for obesity" by Miller *et al*[30] was not obtained, but relevant data from this study was inferred from a 2006 review article. The majority of the studies did not report stimulation parameters (Table 7). Most common forms of pulses reported were "Train of short pulses".

In all studies, the generator was externalized and in most cases they were implanted in subcutaneous layers of the anterior abdominal wall. The electrodes connected to the generator were implanted in different locations of the stomach, depending on the type of GES. TANTALUS® had electrodes in the fundus and antrum. Transcend and RGES had them in the lesser curvature of the anterior medial wall and in the greater curvature of the distal antrum respectively. Gastric pacing had electrodes in either

Table 5 Vagal nerve electrical stimulation studies summary

Ref.	Type of research	Sample size (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/ mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/advice given)	Co-morbidities
Sarr *et al*[34], 2012 [EMPOWER study]	Randomized, Prospective Double blind, Multicentre	294/253	46	NR/41	12	Y/Y	T2DM HTN
Camilleri *et al*[78], 2009	Prospective[1], Multicentre, O	27/25	40.1 ± 1.8	NR/39.3 ± 0.8	6	NR/NR	N
Camilleri *et al*[79], 2008	Prospective, Multicentre, O	31/NR	41.4 ± 1.4	NR/41.2 ± 0.7	6	NR/NR	T2DM

[1]There were two phases in this study. The first one was a retrospective analysis of therapy algorithms used and excess weight loss. The second phase (included in this review data analysis) looked into prospective evaluation of selected therapy algorithms from phase 1. T2DM: Type 2 diabetes.

Table 6 Gastric Pacing studies summary

Ref.[1]	Sample size (enrolled/completed)	Mean age (yr)	Mean weight, (kg)/mean BMI (kg/m^2)	Follow-up (mo)	Lifestyle change (required/ advice given)
Cigaina *et al*[40], 2007	11/11	39.4 ± 3.4	121.7 ± 5.1/46.0 ± 2.5	8	N/Y
Liu *et al*[45], 2006	12/12	29.9 ± 12.3	58.6/21.4	3 d	NR/NR
Yao *et al*[42], 2005	12/12	29.4 ± 8.6	62.6 ± 8.3/23.18 ± 2.62	3 d	NR/NR
Cigaina *et al*[33], 2002	4/3 (1995/6 cohort)	31 ± 10	146 ± 25/55.9 ± 3	60	N/Y
Cigaina *et al*[33], 2002	10/10 (1998 cohort)	34.8 ± 8.6	142 ± 23.75/47.9 ± 5.8	30	N/Y
Cigaina *et al*[33], 2002	10/7 (2000 cohort)	41.8 ± 11.9	131.9 ± 33.1/51.41 ± 9.2	12	N/Y

[1]All trials were non-randomized.

the lesser or the greater curvature.

Regarding outcomes (Tables 8-10), almost all studies in each device group achieved statistically significant weight loss during the first 12 mo. However, only a very small proportion of studies had a follow-up longer than 1 year, and found significant weight loss maintenance.

Other outcomes included appetite or satiety changes and biochemical marker changes. Significant changes in reduction of Hb1Ac levels as well as blood pressure were evident in most TANTALUS® studies and in one IGS study.

Some outcomes were inconsistent. Two studies, one from TANTALUS®[39] and the other from gastric pacing[40], found lower ghrelin levels after device activation. However, three studies, two from IGS[41,42] and another TANTALUS®[43] study, found no statistically significant changes in ghrelin levels. Another interesting find was that 4 studies, including 2 RGES[41,44] studies and 2 gastric pacing[42,45] studies, demonstrated delayed gastric emptying whereas one TANTALUS® study demonstrated the opposite effect.

When the safety of the device implantation procedure was investigated, Transcend®-IGS studies reported the greatest number of device-related, non-medical complications. However, this may be due to the higher number of participants recruited in IGS studies. Gastric penetration was the most common complication during implantation. Even though it may seem to be a very serious complication, all studies reported that all gastric penetrations were corrected immediately and that no serious sequels were caused. Other important complications included lead dislodgement/lead failure and battery problems.

DISCUSSION

Gastrointestinal motility regulates the rates at which nutrients are processed and absorbed. It participates in controlling appetite and satiety *via* mechanical and neurohormone pathways. After bariatric surgery, morbidly obese patients experience reduced appetite and early satiety. These effects are probably related to endocrine effects of surgical procedures. Vertical banded gastroplasty increases post-meal cholecystokinin plasma levels, whereas Roux-en-Y gastric bypass inhibits basal and post-prandial ghrelin plasma levels and increases peptide YY (PYY) concentrations. Jejuno-ileal bypass increases cholecystokinin, motilin, glucagon-like peptide 1 and PYY, delays gastric emptying, and reduces hunger sensations.

As cholecystokinin, ghrelin and PYY also influence gastrointestinal motility, it can be hypothesized that the reduction of gastric emptying could well contribute to the satiety effect of the operations. All these data suggest that reducing gastric emptying could be beneficial for weight loss in patients who follow a strict hypocaloric diet. Modulation of gastric motility could well be a potential target to treat obesity and can be achieved through several means such as volume-occupying devices, intraparietal botox injection and induction of stomach "stiffness"[46-49].

Gastric electrical stimulation (GES) or gastric pacing data from animal models and preliminary data from human trials suggest that the gut-brain axis plays a role in the GES mechanism. This may involve the alteration of the secretion of hormones associated with hunger or satiety. Gastrointestinal tract hormones play a crucial role in regulating energy balance, and manipulation of gut endocrine activity through electrical signaling has been proposed as a potential therapy for obesity[50]. The effects of pacing may depend on stimulus parameters and stimulation sites[51]. Both the entrainment of intrinsic gastric electrical activity, eliciting propagating contractions and reducing symptomatology in patients with gastroparesis,

Table 7 Comparison of stimulation variables by different devices

Device (total number of studies)	Operation technique				Electrode implanted layer							Device active after n weeks				Type of pulse				Endoscopy			Postop image			
	L	O	E	NR	M	SM	Mus	SMus	SS	V	NR	0	⩽ 3 (1 ⩽)	4 ⩽	NR	Lo	T	NR	UC	Y	N	NR	XR	E-US	B	NR
TANTALUS® (8)	8	0	0	0	3	0	0	0	4		1	0	1	6	1	0	0	6	2	3	0	5	1	0	0	7
IGS-Transcend® (13)	12[1]	2[1]	0	1	0	0	2	4	1		5[2] (1[4])	0	4[3]	9[3]	0	0	9	3 (1[4])	0	7	5 (1[4])	0	5	1[5]	1[5]	7 (1[4])
RGES (3)	0	0	3	0	3[6]	3[6]	0	0	0		0	3	0	0	0	2[7]	2[7]	0	0	3	0	0	2	0	0	1
Vagal (3)	3	0	0	0						3	0	0	3	0	0	0	0	0	3	0	0	3	0	0	0	3
Pacing (4)	2[1]	2[1]	2	0	2[6]	1[6]	2	0	0		0	2	0	1	1	2[8]	1[8]	1	1	4	0	0	2	0	0	2
Total (33)	25	4	5	1	8	4	4	4	5	3	6 (1[4])	5	9	16	2	4	12	10 (1[4])	6	17	5 (1[4])	8	10	1	1	20 (1[4])

[1]Two studies implanted leads either by laparoscopic or open approach; [2]Two studies reported "gastric wall", but did not specify which particular layer; [3]One study activated its device after 3 or 4 wk, so each category was counted once; [4]No full text for LOSS trial, and this information was also not provided on another study, which reviewed this particular trial; [5]One study did both X-ray and endoscopic USS. Similarly another study did both X-ray and GI Barium test; [6]Implanted electrodes in mucosa and submucosa (3 studies in RGES; 1 study in Gastric Pacing); [7]One study carried out two different pulses; [8]One study carried out two different pulses. L: Laparoscopic; O: Open; E: Endoscopic; NR: Not reported; M: Mucosa; SM: Submucosa; Mus: Muscular; SMus: Seromuscular; SS: Subserosa; V: Vagal nerve; Lo: Long pulse; T: Train of short pulses; UC: Uncertain; Y: Yes; N: No; XR: X-ray; E-US: Endoscopic ultrasound scan; B: Gastrointestinal Barium test.

and reducing appetite and food intake in morbid obesity were suggested[52]. Additionally, gastric stimulations have extra gastrointestinal effects, including the alteration of systemic hormonal and autonomic neural activity and the modulation of afferent nerve pathways projecting to the central nervous system. These devices require a laparoscopic procedure to be implanted. Overall results suggest a short-term excess weight loss of approximately 40%[32].

The concept of electrical stimulation of electro-sensitive tissues is not new. It has been used for centuries in physiology studies and has a potential therapeutic strategy. Deep brain stimulation is used to treat Parkinson's disease. Neuromodulators can improve chronic non-malignant pain, and sacral nerve electrical stimulation can restore bladder function in refractory voiding dysfunction[53]. Colonic pacing has been used to induce rectal motility and evacuation in patients with colonic inertia, suffering from slow-transit constipation[54].

With much use of electrical stimulation in various medical fields in the past and recent promising results from many animal experiments, it appears that GES was the most effective and appropriate choice to reverse the increasing incidence of obesity and its related health co-morbidities.

Unlike cardiac pacemakers which can bring about a rapid response from cardiac muscles and nerves, the smooth muscles in the stomach slow down the response to electrical stimulation, forcing stimulations to have either longer or wider pulses[10].

In an experimental study, it was found that an intrinsic gastric pacemaker was present between the upper one third and lower two thirds of the stomach, on the upper part of the lesser curvature[55]. Gastric pacing at these locations has demonstrated the following effects: reduced appetite, increased satiety, inhibition of gastric motility. In addition, it directly affected central nervous system mechanisms and gastric hormones controlling satiety and appetite[55].

To date, several different types of GES have been developed. The most widely known commercial ones are the following[22]: (1) TANTALUS® system (MetaCure, Atir Yeda 17 Kfar Saba, Israël); (2) Enterra® Therapy (Medtronics, United States); (3) Transcend® Implantable Gastric Stimulator (Medtronic Transneuronix, United States); (4) Maestro® rechargeable system (EnteroMedics, United States)-electrical stimulation of the vagal nerve; and (5) Acupulser model A310, (World Precision Instrument, Sarasota, FL, United States)-Retrograde electrical stimulation.

The first human use of GES was for the treatment of gastroparesis in Tennessee in 1992, and its use for obesity soon followed in Italy in 1995[56]. While the GES device for the treatment of nausea and vomiting in patients with gastroparesis, called Enterra®, is FDA-approved, none of the GES devices have obtained FDA approval to treat obesity as of yet[57]. However, commercially available GES devices such as TANTALUS®, Transcend® and Maestro® are used clinically in Europe[56].

The exact mechanisms of action of GES are still unknown[24,26]. Some potential mechanisms of GES include a local enteric nervous system effect influenced by changes in gastric volume, an autonomic nervous system that can have different effects depending on frequency, a central nervous system and peptide hormonal changes in cholecystokinin (CCK), ghrelin, leptin, glucagon-like peptide-1 (GLP-1), and somatostatin[56,58].

Table 8 Comparison of outcomes of different devices (statistically significant outcomes only)

Device (total number of studies)	Significant weight loss achieved ≤ 12 mo (number of trials)	Follow-up beyond 12 mo and significant weight loss maintained from the first 12 mo (number of trials)[1]	Appetite reduction/satiety increase (number of trials)	Food and/or water intake reduction, comparing study group to control (number of trials)	Changes in gastric emptying (number of trials)	Biochemistry changes reported (number of trials)[4]
TANTALUS® (8)	6[2]	None (maximum of 12 mo follow-up)	2 (25%)		Increased (1)	4[5]
IGS-Transcend (13)	10[3]	5	3 (23%)			1
Vagal stimulation (3)	2	None (maximum of 12 mo follow-up)	3 (100%)			1
Gastric Pacing (6)	4	2		2	Delayed (2[6])	1
Total (30)	22	7	8 (26.6%)	3	5	7

[1]Maintained weight loss means that studies had shown significant weight loss during the first year of their follow-up; [2]One study showed a weight loss of 3.62% from baseline at 37 wk, but p value was not given, so this was not included in the count; [3]One study demonstrated significant weight loss at 12 mo only after procedural correction; [4]Significant biochemistry changes include any gastrointestinal hormones (such as ghrelin, peptide YY, leptin, somatostatin, cholecystokinin, Glucagon-like Peptide-1), HbA1c, fasting blood glucose, cholesterol; [5]One study showed a reduction of -12.2% in HbA1c levels at 37 wk but *P* value was not given so it was not included in the count; [6]In one study, gastric emptying was achieved only after 45 min, and there was no significant delaying afterwards.

In order to achieve weight loss, one or more of the following processes should be achieved by the neurohormones[50]: (1) GLP-1 (incretin hormone found in the lower gut) must be increased in response to food intake in order to delay gastric emptying; (2) Leptin (coded by the ob gene, found in adipose tissues) must be increased to induce food intake reduction, improve glucose homeostasis, and increase energy expenditure; and (3) Peptide YY (PYY, gut hormone found in L cell of lower intestine) changes its form to PYY 1-36 in fasting state and to PYY 3-36 in post-prandial state. Its increased level can inhibit gastric motility to reduce hunger and consequently reduce food intake. It also results in better glucose homeostasis, secondary to increased insulin sensitivity as well as reduction in triglyceride and fatty acid levels: (1) CCK (produced by endocrine cells in the small intestine) must be increased to reduce food intake *via* CCK-1 receptors in vagus nerves; and (2) Ghrelin (produced by cells in the oxyntic glands of the stomach and intestines) must be reduced to decrease food intake and lose body weight.

Ghrelin is the only known peripheral orexigenic peptide hormone[50,58]. If its level can be lowered, it can achieve appetite reduction, and therefore weight loss. A number of studies routinely measured ghrelin levels, but the results were inconsistent as some studies found significantly lowered ghrelin level after GES, while others failed to demonstrate any significant changes[36,43].

In the present review, we aimed to focus on GES devices and we tried to analyze available evidence on a larger group of GES devices to obtain a general overview. Globally, we found many variations and much heterogeneity in the reported studies concerning the type of device, stimulation parameters and outcomes. It was therefore difficult to report data in a standardized way, especially when trying to correlate stimulation parameters and outcomes.

Technical considerations

Implantation: The most common electrode implantation procedure was by laparoscopic surgery. Electrodes were most frequently implanted in the mucosa of the stomach wall. However, TANTALUS® and Transcend® were more frequently implanted in the submucosa and seromuscular layers. Generators were implanted in a subcutaneous pouch on the anterior abdominal wall. The mucosa has a higher impedance than the serosa, limiting the spread of electrical stimuli into muscular and neural networks in the stomach[22]. However, the correct placement through the different layers was checked by means of perioperative endoscopy, which can be less accurate than electrophysiology or image-guided testing (such as high frequency endoscopic ultrasound).

Stimulation parameters (Table 7): In general, participants were given 4 or more weeks of recovery time before starting the stimulation.

The "optimal stimulation pattern" has not yet been found. There are three stimulation methods-long pulse, short pulse, and trains of short pulses. The long pulse has the ability to "pace" or entrain a natural slow wave with a pulse width in the order of milliseconds and a frequency that is close to the physiological frequency of the gastric slow wave[10]. Gastric pacing uses long pulses but there are currently no implantable pulse generators that can produce pulses with a width longer than 2 milliseconds[10]. Long pulses generally improve symptoms of nausea and vomiting while having little effect on gastric motility. Conversely, long pulses improve gastric motility but are less effective when it comes to nausea and vomiting management[10].

Trains of short pulses consist in continuous short pulses with a high frequency (5-100 Hz) and a control signal to turn pulses on and off[10]. IGS-Transcend® by Medtronics uses this method to induce early satiety with subsequent reduction of food intake and weight loss, but it has failed to show consistent and positive weight loss in obese patients[57] and requires more powerful devices with a wider pulse width as suggested in one review[10,57]. Short

Table 9 TANTALUS® studies significant outcomes

	Weight, kg	Average Weight loss, kg (%)			HbA1c (%)	Average HbA1c reduction, % (% change)			Other statistically significant or important negative results[3]
	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	
T1[38]	110.5 ± 3.5		-5.38 (-4.87%), P < 0.01		8.3% ± 0.12%		-1.0 (-12.0%), P < 0.001		Lower BP (S/D)
T2[70]	107.7 ± 21.1 (n = 11)	-3.00 (-2.79%), P < 0.05	-5.30 (-4.92%), P < 0.05		8.5% ± 0.7%	-1.0 (-11.8%), P < 0.05	-0.9 (-10.6%), P < 0.05		Lower BP (S) Lower total cholesterol Lower LDL
T3[39]	123.7 ± 4.5		-5.80 (-4.70%), P < 0.05 at 5 mo	-4.50 (-3.70%) [P < 0.05]	8.0% ± 0.2%		-0.6 (-7.5%), P < 0.05 at 5 mo	-0.5 (-6.3%), P < 0.05	Lower FBG Lower ghrelin[4] Higher adiponectin[4] Reduced appetite[2] (P < 0.05)
T4[37]	NR		-5.50 (P < 0.01)		8.4% ± 0.1%		-1.1 (-12.1%), P < 0.01		Lower BP if hypertensive at baseline
T5[71]	104.4 ± 4.4	-4.70 (-4.52%), P < 0.001			8.0% ± 0.2%	-1.1 (-12.8%), P < 0.001			Lower BP (S/D) Lower FBG
T6[69]	130 ± 6.5			-4.70 (-3.62%) (P value NR) at 37 wk	8.2% ± 0.2%			-1.0 (-12.2%) (P value NR) at 37 wk	
T7[43]	NR								Increased GE Reduced gastric retention (No significant changes in Ghrelin)
T8[72]	128.8 ± 5.2		-8.90 (-6.91%), P < 0.05 at 5 mo	-16.4 (-12.7%) (P value NR)[1]					Lower BP if hypertensive at baseline Reduced appetite (P < 0.05)

[1]Only 9 out of 12 subjects remained by the 12th month; [2]Except from week 20 to week 52, there was a slight increase (P = NS) in hunger score, but otherwise, all scores were significant (P < 0.05); [3]Significant results in reference to baseline values; [4]Results based on a smaller subset of participants. BP: Blood pressure; LDL: Low-density lipoproteins; FBG: Fasting blood glucose.

pulses or trains of short pulses fall into the category of low energy/high frequency stimulation which does not entrain slow wave or improve gastric emptying. High energy/low frequency stimulation does entrain slow wave or correct gastric dysrhythmia, but it does not allow for the potential improvement of gastric emptying. However, as abovementioned, there is no commercially available implantable long pulse device as of yet[59]. Enterra® uses short pulses, namely a pulse width of a few hundred microseconds, and a frequency higher than the physiological frequency of the gastric slow wave[60]. Commercially available cardiac pacemakers or nerve stimulators also use short pulses.

Different types of stimulation also have varying effect on weight loss. Antegrade stimulation propagates its impulses in a forward direction, and works more effectively on the gastroparetic stomach. On the other hand, retrograde stimulation affects conduction of slow wave activity of the gastric smooth muscle in the opposite direction to antegrade, thereby slowing gastric emptying and inducing more active weight loss. However, it all depends on the setting. The technical aspects of devices are not discussed in this review as they have been extensively tackled previously in other recent reviews on GES.

General considerations on studies and outcomes of the most relevant studies

The level of evidence is generally quite low. Most studies were non-randomized trials and only a few studies had a large population size with low drop-out rates. Many studies included either healthy volunteers or subjects who only had obesity. In contrast, TANTALUS® studies included obese patients with co-morbidities such as type 2 diabetes and hypertension. As a consequence, the majority of TANTALUS® studies reported on HbA1c levels in addition to weight loss (Table 9).

Weight loss was the primary outcome, but follow-up generally lasted less than 12 mo and maintenance of significant weight loss was rarely observed. Only one study[28,39] reported significant weight loss at both 6 and 12 mo. However, 6-mo weight loss was greater than that achieved at a later time period. This might mean that GES may not induce long-term weight loss and that some patients may lose weight due to other variables such as postoperative effects.

One valuable screening tool is the Baroscreen™, trademarked by Medtronic Transneuronix, Inc. The Baroscreen™ is a computer software which measures the suitability of obesity therapy through a mathematical algorithm and allows to select patients who are most likely to lose ⩾ 15% excess bodyweight within 12 mo. The Baroscreen™ was applied to some Transcend®-IGS studies (n = 4). In two studies[15,28], significant weight loss was observed while in other studies[21,29] no significant weight loss was reported. Some of the IGS studies also required their subjects to have a specific diet and exercise regimen,

Table 10 Implantable Gastric Stimulator Transcend® outcomes

	Weight, kg	Average Weight loss, kg (%)-In the treatment group compared to baseline weight				Hunger reduction/ Reduced appetite	Other statistically significant or important negative results[3]
	Baseline	At 3 mo ± 2 wk	At 6 mo ± 2 wk	At 12 mo ± 3 mo	Beyond 12 mo		
I1[28]	113.1		-7.0 (-6.2%), $P < 0.05$	-5.5 (-4.9%), $P < 0.05$	-2.1 (-1.9%), $P < 0.05$ at 24 mo		In control group, weight gain despite IGS activation from 12 to 24 mo No significant change in fasting ghrelin or Peptide YY levels
I2[21]	NR						No significant weight loss observed
I3[73]	112.5		-2 (-1.8%) NS	+3.5 (+3.1%) NS			No significant weight loss observed
I4[29]	92		%EWL = 5.9%				
I5[30]	116	%EWL = 14%	%EWL = 19%	%EWL = 20%	%EWL = 25%		
I6[20]	129		%EWL = 1.3% (study group); 2.4% (control) NS	Mean %EWL = 2.5% (P value NR)	%EWL = 20% at 29 mo[1]		Only a subset (23%) of patients lost significant amount of weight (> 5% EWL)
I7[20]	NR			%EWL > 10% in 54% of subjects; > 20% in 23%	%EWL = 23% at 16 mo	Yes[2], $P = 0.0433$	Satiety increased between and at the end of meals
I8[32]	132.7± 27.3	%EWL for 2 yr period for each cohort = 20%-40%					Lower blood pressure
I9[74]	115	%EWL = 16.3% -8.2 (-7.11%), $P = 0.0011$	%EWL = 16.9% -8.4 (-7.29%), $P = 0.0310$	%EWL = 23.8% at 10 mo -11.7 (-10.1%), $P = 0.0112$		Yes	Satiety increased between and at the end of meals
I10[36]	115	%EWL = 15.8%	%EWL = 17.8%	%EWL = 21.0% at 10 mo	%EWL = 21.0% at 15 mo	Yes	Satiety increased between and at the end of meals No significant change in ghrelin level
I11[75]	121.7± 5.1		-10.4 (-8.5%), $P < 0.01$				Reduced meal-related CCK response Lower basal and meal-related somatostatin level Lower basal GLP-1 level (Not meal-related) Lower basal leptin level (Not meal-related)
I12[35]	NR			-2.7%, $P = 0.03$			Significant weight loss at 12 mo was observed after procedural corrections
I13[76]	122.2	%EWL = 17.8% -9.4 (-7.7%) (P value NR)	%EWL = 18.6 -10.0 (-8.2%) (P value NR)	%EWL 30.2 at 9 mo -16.0 (-13.1%) (P value NR)			

[1]Very small number of remaining subjects ($n = 34$); [2]Responses to the Satiety and Dietary Analysis Questionnaire; [3]Significant results in reference to baseline values. NR: Not reported; EWL: Excess weight loss; CCK: Cholecystokinin; GLP-1: Glucagon like peptide-1.

but this did not mean that the outcome was necessarily better. Two studies[21,28] required patients to have a 500 kcal/d deficit diet, and participate in monthly support group meetings. One study[29] required a 500 kcal/d deficit diet with an exercise program. Another[20,31] required patients to complete the LEARN Behavior Modification Program and to attend monthly support group meetings. Diet and behavior modification had only a very mild short-term impact. Considering that diet and exercise only have a short-term effect, it is logical to assume that its effect on weight loss may be negligible in the long term.

Generally speaking, the majority of bariatric interventions, whether surgical or not, including procedures for GES device implantation, induce effective short-term weight loss. Therefore, follow-up periods to assess weight loss modalities should be relatively long to eliminate confounding effects from any dietary or behavioral change that some patients may undergo at the beginning of their treatment.

An additional problem with long-term follow-up is that in battery-operated devices, the battery may run out and lead to weight regain[24]. In a case series, patients followed up for approximately 10 years underwent repeated surgery for battery replacement[61]. Battery lifetime is approximately 2 to 5 years, which implies inevitable repeated procedures in relatively short intervals[11]. An improvement of battery technology for longer-lasting batteries and in the battery life monitoring method, are clearly required in order to sustain long-term weight loss,

and enhance the role of GES in obesity.

Other commonly reported outcomes included appetite reduction/satiety increase, gastric emptying rate change and gastric hormonal or other biochemical markers such as ghrelin and HbA1. Blood pressure was also monitored in the majority of TANTALUS® and in some Transcend® studies. In almost all cases, the decrease in blood pressure was more pronounced if patients were hypertensive at the start of the trial. This led to a theory that GES influences the autonomic nervous system[32] but the exact physiology has not been studied.

Safety and adverse events

Despite the fact that GES implantation is less invasive than bariatric surgery, it still requires an operation with general anesthesia. Although all devices were deemed to be safe as there were no serious complications or deaths from procedures, the absolute numbers for device-related complications such as gastric penetration and lead dislodgement were relatively high. Out of the two complications, gastric penetration was the most frequent one. It appeared to happen more often when the implantation involved either the subserosa or seromuscular layers. Gastric penetrations were corrected surgically in all cases, and no further serious complications occurred postoperatively. This potential complication stresses the need for intraoperative endoscopy during or after lead implantation as a crucial part of the procedure[62]. Postoperative complications such as nausea, constipation, and hypoglycemia were rare and could be minimized by careful monitoring, and by optimizing medical treatments, controlling pain with analgesics and assessing the functional status of each patient properly prior to discharge[62].

Other forms of electrical stimulations have also been reported in the literature. Intestinal electrical stimulation (IES) is used in the duodenum or the colon. It affects intestinal slow waves, contractions and transit through vagal and cholinergic and adrenergic pathways[22]. Just like GES, there are various types of pulses for IES such as long pulse, short pulse, train of short pulses, dual pulses and synchronized pulse stimulation. Numerous studies have been carried out mainly in canine subjects while only two studies[63,64] were performed in humans. One study demonstrated accelerated intestinal transit and reduced absorption in patients with lipid infusion[63], and another demonstrated delayed gastric emptying and reduced gastric accommodation[64]. In animal experiments, more comprehensive effects were observed. In rats, IES reduced food intake and bodyweight in both lean and obese rats, decreased ghrelin levels and increased CCK in duodenal tissues[65]. In dogs, IES induced gastric distension, which then reduced food intake[65].

In contrast to GES, IES uses repetitive long pulses with a frequency lower than 1 Hz in order to accommodate slow response time of intestinal smooth muscle to electrical stimulation[66]. It has been shown to entrain intrinsic intestinal slow waves and improve intestinal slow wave dysrhythmia in animals, but due to the lack of data from patients, more clinical trials must be performed before determining its effectiveness as a therapy for obesity[66].

Recommendations and future perspectives

The concept of gastric electrical stimulation itself seems to hold some promises. However, it has so far been shown that weight loss with GES is lower than that observed with current bariatric surgeries, but greater than that achieved with non-medical and behavioral modifications[67]. There are too many differences in the studies performed to date: different device parameters, different implantation sites and outcomes measured. This can only lead to a situation where studies are not comparable and high quality studies on GES and obesity do not exist to this date. The main reason to perform clinical trials on GES is to prove that GES is not inferior to bariatric surgery, which is the only effective treatment, but carries more risks due to the invasive nature of surgical procedures[68].

However, in order to be effective, GES should be tailored to each patient. The main drawback in the performed studies, from a purely physiological standpoint, is that electrodes are placed "somewhere" in the stomach where the pacemaker is supposed to generate contraction waves. It would be correct to generate the hypothesis that gastric pacemaker location varies from one patient to another, as well as sensitivity of the pacemaker to electric stimuli. The introduction of functional imaging modalities are generated, such as real-time Magnetic Resonance Imaging or intragastric electrode which allow to exactly locate the waves could well optimize the placement of electrodes or other different stimulation/blocking modalities.

Larger populations should be included in prospective trials in which electrical pulse properties and anatomical stimulation sites have been pre-determined in each patient prior to the procedure. Inclusion criteria should also be standardized, for example using tools such as the Baroscreen™, in order to stratify patients and obtain results which could be compared with other studies[52]. The follow-up period must be longer to minimize any placebo effect[69] and to prove that weight loss can be maintained for a longer period of time than weight loss induced by non-medical and medical interventions.

In addition, a GES device monitoring tool should be considered to improve the ease of use and the interaction between the device and patients, similarly to a cardiac pacemaker that patients can monitor using a telephone[54]. In terms of GES device, the ideal device should ultimately be implantable endoscopically (without having to undergo general anesthesia or any form of surgery), it should control the electrode and stimulation generator wirelessly in order to be connected without having to externalize the wire, and as mentioned above, stimulation parameters should be controlled and be recorded by a portable device that people could carry around with them, such as a mobile phone.

This systematic review presents the most up-to-date review of the literature on the effects that different GES devices have on obesity. Although not all the studies have shown consistent results, many studies have demonstrated that GES is effective for short-term weight control as well as for the change of other variables associated with obesity. However, well-designed, standardized clinical trials with a larger sample size and a longer follow-up period should be considered to prove its true benefit for the treatment of obesity and further advancement in GES device technology should continue to take place.

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COMMENTS

Background

Overweight and obesity, as a major health concern, have become a global issue. Lifestyle and medical measures are effective in the short term but maintenance of weight loss in the long term has proven to be difficult. On the other hand, surgical interventions are more effective in the long run but they have a higher risk of complication rates.

Research frontiers

Gastric Electrical Stimulation (GES) has shown to be more effective than lifestyle and medical options to treat obesity while having a lower risk of complications than bariatric surgery. The first use of GES was to treat gastroparesis in 1992, and its use for obesity soon followed in Italy in 1995.

Innovations and breakthroughs

GES for obesity is a method of provoking gastric contractions and inducing longer retention of food in the stomach to cause early satiety and therefore reduce food intake. Currently, there are many commercially available GES devices used clinically mostly in Europe. However, they do not benefit from FDA approval. Due to a wide range of existing devices with much variation in their type, stimulation parameters and study outcomes, it is difficult to report the combined data in a standardized way. Clinically, weight loss was achieved in most studies especially during the first 12 mo and studies with a longer follow-up period showed promising results in maintaining weight loss. Other positive outcomes reported were increase in satiety, decreased gastric emptying rate, reduced blood pressure, and changes in neurohormone or biochemical marker levels such as ghrelin or HbA1c.

Applications

This systematic review is the most up-to-date summary of the literature on the effects that different GES devices have on obesity by comparing their study designs, stimulation parameters, and reported outcomes. It also suggested that future studies should consider putting forward stronger evidence concerning GES benefit on obesity and making further advancements in GES technology.

Peer review

In this study, the authors made a systemic review on the GES to treat obesity, which evaluated the current state of GES application in clinic for treating obesity. It provided benefited reference for the clinical physicians and scientists.

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CLINICAL TRIALS STUDY

Analysis of YouTube™ videos related to bowel preparation for colonoscopy

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Abstract

AIM: To examine YouTube™ videos about bowel preparation procedure to better understand the quality of this information on the Internet.

METHODS: YouTube™ videos related to colonoscopy preparation were identified during the winter of 2014; only those with ≥ 5000 views were selected for analysis (n = 280). Creator of the video, length, date posted, whether the video was based upon personal experience, and theme was recorded. Bivariate analysis was conducted to examine differences between consumers *vs* healthcare professionals-created videos.

RESULTS: Most videos were based on personal experience. Half were created by consumers and 34% were ≥ 4.5 min long. Healthcare professional videos were viewed more often (> 19400, 59.4% *vs* 40.8%, P = 0.037, for healthcare professional and consumer, respectively) and more often focused on the purgative type and completing the preparation. Consumer videos received more comments (> 10 comments, 62.2% *vs* 42.7%, P = 0.001) and more often emphasized the palatability of the purgative, disgust, and hunger during the procedure. Content of colonoscopy bowel preparation YouTube™ videos is influenced by who creates the video and may affect views on colon cancer screening.

CONCLUSION: The impact of perspectives on the quality of health-related information found on the Internet requires further examination.

Key words: Colon cancer prevention; Bowel preparation; Colonoscopy; Screening; YouTube™; Social media

Core tip: YouTube™ is a major media channel viewed by millions each day. Despite this reach, there is a paucity of research on the nature and scope of communications related to cancer prevention and control. To our knowledge, this is the first published study analyzing communications through YouTube™ concerning bowel preparation. The content of the YouTube™ videos regarding colonoscopy bowel preparation is influenced by who creates the video. Consumer posted videos generated the majority of comments on this topic.

Basch CH, Hillyer GC, Reeves R, Basch CE. Analysis of YouTube™ videos related to bowel preparation for colonoscopy. *World J Gastrointest Endosc* 2014; 6(9): 432-435 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i9/432.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i9.432

INTRODUCTION

The Internet has become an increasingly popular source

of health information for consumers. With over half of United States Internet users searching for information on a specific medical procedure, the quality of information available and its impact on the public's thoughts are significant[1]. YouTube™ has monthly traffic volume of about 1 billion users and provides a unique platform for conveying health information where both consumer and professional videos can be accessed[2]. Despite widespread reach, limited research on this communication channel has been conducted to characterize the source and content of information conveyed.

The purpose of this study was to analyze source and content of information conveyed in frequently viewed YouTube™ videos about preparing for a colonoscopy. Colon cancer screening is an important preventive measure, which is recommended by the United States Preventive Services Task Force[3]. The American College of Gastroenterology has recommended CRC screening by colonoscopy as the preferred screening modality[4]. Despite the existence of these recommendations, rates of CRC screening in general and colonoscopy screening in particular are less than optimal[5]. One reason for this may be that preparing for a colonoscopy is typically considered the "worst part" of the colonoscopy procedure[6]. Inadequate bowel preparation, which has been shown to occur in as many as 20% of colonoscopies[7], can obscure vision, and pre-cancerous or cancerous polyps can be missed[7,8].

MATERIALS AND METHODS

Between January and February 2014, the YouTube™ website was searched using the following keywords: colonoscopy preparation (19000 videos), colonoscopy prep (5140 videos), colon prep (7570 videos), colon preparation (7950 videos), bowel preparation (1770 videos) and bowel prep (7770 videos). All videos were sorted to determine how many had over 5000 views and duplicate videos were removed (n = 280). Videos with the highest number of views were screened to verify that the focus was on preparation for colonoscopy. The source of each video was coded as being created by a consumer or a professional. We identified 98 videos created by consumers and 96 videos created by professionals that had ⩾ 5000 views, which were selected for analysis. These videos were coded based on total number of views received and subject matter. Subject matter coding included whether the topic was addressed by relating a personal experience, general information, completing the preparation, types of preparation, palatability, pain, time required, disgust, embarrassment, sleep deprivation, hunger, difficulty and fear. The length of each video was documented along with the time elapsed since it was uploaded and the number of comments recorded. These methods were piloted on 10 videos with fewer than 5000 views, which were not included in our sample. Coding of the videos was conducted by one of the authors (RFR) and by another author (CHB) for the 50 videos that received the most views. High inter-rater reliability was demonstrated using Cohen's Kappa (k = 0.89).

Table 1 Characteristics of YouTube™ videos (n = 194) of colonoscopy bowel preparation n (%)

	Total (n = 194)	Consumer (n = 98)	Healthcare professional (n = 96)	P value
Year video uploaded				0.14
2006	5 (2.6)	4 (4.1)	1 (1.0)	
2007	14 (7.2)	7 (7.1)	7 (7.3)	
2008	25 (12.9)	12 (12.2)	13 (13.5)	
2009	48 (24.7)	25 (25.5)	23 (24.0)	
2010	29 (14.9)	10 (10.2)	19 (19.8)	
2011	39 (20.1)	16 (16.3)	23 (24.0)	
2012	25 (12.9)	18 (18.4)	7 (7.3)	
2013, 2014	9 (4.6)	6 (6.1)	3 (3.1)	
Time since posting (mo)				0.31
0-36 (2011-2014)	73 (37.6)	40 (40.8)	33 (34.4)	
37-48 (2010)	29 (14.9)	10 (10.2)	19 (19.8)	
49-60 (2009)	48 (24.7)	25 (25.5)	23 (24.0)	
> 60 (2006-2008)	44 (22.7)	23 (23.5)	21 (21.9)	
Length of video (min)				0.45
0.0-1.5	46 (23.7)	21 (21.4)	25 (26.0)	
1.6-3.0	42 (21.6)	18 (18.4)	24 (25.0)	
3.1-4.5	40 (20.6)	23 (23.5)	17 (17.7)	
> 4.5	66 (34.0)	36 (36.7)	30 (31.3)	
Number of video views				0.037
5028-13300	48 (24.7)	32 (32.7)	16 (16.7)	
13301-18400	49 (25.3)	26 (26.5)	23 (24.0)	
18401-66500	49 (25.3)	20 (20.4)	29 (30.2)	
66501-3933235	48 (24.7)	20 (20.4)	28 (29.2)	
Views per month				0.18
0-250	52 (26.8)	32 (32.7)	20 (20.8)	
251-500	40 (20.6)	21 (21.4)	19 (19.8)	
501-2000	59 (30.4)	28 (28.6)	31 (32.3)	
> 2000	43 (22.2)	17 (17.3)	26 (27.1)	
Number of comments				0.001
0-3	53 (27.3)	16 (16.3)	37 (38.5)	
4-9	39 (20.1)	21 (21.4)	18 (18.8)	
10-40	44 (22.7)	31 (31.6)	13 (13.5)	
> 40	58 (29.9)	30 (30.6)	28 (29.2)	
Comments per month				0.09
< 1	130 (67.0)	60 (61.2)	70 (72.9)	
1-2	26 (13.4)	18 (18.4)	8 (8.3)	
> 2	38 (19.6)	20 (20.4)	18 (18.8	

Descriptive analyses included frequencies, percentages, means, standard deviations, and ranges. Length of time since posting in months, length of the video in minutes, number of views, overall and per month, and total number comments were grouped by quartile. Analysis was performed using Chi-square for categorical variables and ANOVA for continuous variables. One-sided p values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS (version 21). All study procedures were reviewed by the institutional review boards of the authors' respective institutions and were deemed not related to human subjects.

RESULTS

Consumers and healthcare professionals each created approximately one-half of the videos (Table 1). Videos

Table 2 Themes of YouTube™ videos *n* (%)

	Total (*n* = 194)	Consumer (*n* = 98)	Healthcare professional (*n* = 96)	*P* value
Based on personal experience				0.18
Yes	114 (58.8)	53 (54.1)	61 (63.5)	
No	80 (41.2)	45 (45.9)	35 (36.5)	
Themes				
General information				< 0.001
Yes	79 (40.9)	12 (12.4)	67 (69.8)	
No	114 (59.1)	85 (87.6)	29 (30.2)	
Completing the preparation				< 0.001
Yes	43 (22.2)	11 (11.2)	32 (33.3)	
No	151 (77.8)	87 (88.8)	64 (66.7)	
Types of preparation				< 0.001
Yes	20 (10.3)	3 (3.1)	17 (17.7)	
No	174 (89.7)	95 (96.9)	79 (82.3)	
Palatability				0.048
Yes	55 (28.4)	34 (34.7)	21 (21.9)	
No	139 (71.6)	64 (65.3)	75 (78.1)	
Pain				0.78
Yes	23 (11.9)	11 (11.2)	12 (12.5)	
No	171 (88.1)	87 (88.8)	84 (87.5)	
Time involved				0.68
Yes	49 (25.3)	26 (26.5)	23 (24.0)	
No	145 (74.7)	72 (73.5)	73 (76.0)	
Disgust				0.009
Yes	19 (9.8)	15 (15.3)	4 (4.2)	
No	175 (90.2)	83 (84.7)	92 (95.8)	
Embarrassment				0.08
Yes	17 (8.8)	12 (12.2)	5 (5.2)	
No	177 (91.2)	86 (87.8)	91 (94.8)	
Sleep deprivation				0.06
Yes	10 (5.2)	8 (8.2)	2 (2.1)	
No	184 (94.8)	90 (91.8)	94 (97.9)	
Hunger				0.009
Yes	19 (9.8)	15 (15.3)	4 (4.2)	
No	175 (90.2)	83 (84.7)	92 (95.8)	
Difficulty to perform				0.65
Yes	18 (9.3)	10 (10.2)	8 (8.3)	
No	176 (90.7)	88 (89.8)	88 (91.7)	
Fear				0.71
Yes	26 (13.4)	14 (14.3)	12 (12.5)	
No	168 (86.6)	84 (85.7)	84 (87.5)	

were uploaded between 2006 and 2014, with the majority (79.3%) posted after 2008. Just over one-third of the videos were > 4.5 min (SD 5.3) in length (range 0.4 to 53.3 min), with the remaining videos distributed fairly evenly across the three other categories. Combined, there were more than 12.7 million views of the sampled videos. The number of views per video varied greatly and was dependent upon the length of time the video was available for viewing (overall range 5028 to 3.9 million views, range per month 91 to 57003). The number of comments also differed widely overall, ranging from no comments posted to nearly 3000. The mean number of comments per month was 1.3 (SD 4.1).

Overall, healthcare professional-generated videos had greater numbers of views than did those created by consumers (> 19400, 59.4% *vs* 40.8%, $P = 0.037$, for healthcare professional and consumer, respectively). In contrast, videos created by consumers received more comments (> 10 comments, 62.2% *vs* 42.7%, $P = 0.001$). When examining the number of views and comments per month, this difference was no longer observed. Additionally, no differences between videos created by consumers *vs* healthcare professionals were observed for the year of posting or length in minutes.

Almost 60% ($n = 114$) of all of the videos sampled were based on personal experience, and there was no significant difference regarding this appeal based on the source of the communication (Table 2). Compared with consumer created videos, those created by healthcare professionals were much more likely to provide general information about the preparation process, (12.4% *vs* 69.8%, $P < 0.001$), include information about completing the preparation process (11.2% *vs* 33.3% $P < 0.001$), and the types of preparation options that are available (3.1% *vs* 17.7% $P < 0.001$). Overall, only approximately 10% of the videos addressed the different types of preparation purgatives, disgust, embarrassment, hunger, difficulty, and fear and only approximately 5% dealt with the topic of sleep deprivation. There were no significant differences between the videos created by consumers *vs* healthcare professionals with respect to palatability of the purgative, pain, time involved, embarrassment, sleep deprivation, difficulty, and fear. In contrast, compared with videos created by healthcare professionals, those created by consumers were more likely to address topics related to palatability of the purgative (21.9% *vs* 34.7%, $P < 0.05$), disgust (4.2% *vs* 15.3%, $P < 0.01$), and hunger (4.2% *vs* 15.3%, $P < 0.01$).

DISCUSSION

The clinical and public health benefits of colonoscopy screening can be compromised by poor quality preparation[7,9-11] as well as adding cost, risk and inconvenience due to repeated procedures[12]. Suboptimal preparation is not a rare occurrence[13,14] and appears to be more likely among those at greater risk for late stage of diagnosis and consequently worse prognosis[13]. Efforts to promote adequate (or ideally optimal) preparation are, therefore, warranted. Social media such as YouTube™ is a communication channel that is increasingly used by the public to acquire health information in general and colonoscopy preparation specifically.

This was the first study to assess colonoscopy preparation information on YouTube™. This sample of videos collectively had nearly 13 million views. Many of the videos were related to personal experience. Some important topics (*e.g.,* types of preparation purgatives, disgust, embarrassment, hunger, difficulty, fear and sleep deprivation) were not addressed by majority of the videos reviewed. Social media has both the promise of reaching a very large audience with important information, but may also provide misinformation. Even if the information conveyed is accurate, it may negatively influence views on colon cancer screening. Future studies are needed to verify the accuracy of information about colonoscopy

preparation and to assess the perspectives conveyed. Social media is currently underutilized by governmental agencies to convey important health information about colonoscopy preparation and this is a missed opportunity to provide accurate and accessible information to the public about this important public health topic.

COMMENTS

Background

Colonoscopy has emerged as the preferred colon cancer screening method. Bowel preparation for colonoscopy has been described as the worst part of the procedure. Many people seek health information from media outlets like YouTube™.

Research frontiers

To date, there are no published papers examining the content of these videos related to bowel preparation for the colonoscopy procedure.

Innovations and breakthroughs

There were no other studies on this topic identified in the published literature. This is an innovative study in that it is the first in the published literature to analyze source and content of information conveyed in frequently viewed YouTube ™ videos about preparing for a colonoscopy.

Applications

The practical applications of these findings are that endoscopists should be aware of misinformation that may impact beliefs and practices of a patient regarding colonoscopy preparation.

Terminology

YouTube™ is a popular video-sharing web site based in the United States.

Peer review

The results of present study have new and original finding. The study has been thought very well and its design is good.

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SYSTEMATIC REVIEWS

Evaluation of surgical training in the era of simulation

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Abstract

AIM: To assess where we currently stand in relation to simulator-based training within modern surgical training curricula.

METHODS: A systematic literature search was performed in PubMed database using keywords "simulation", "skills assessment" and "surgery". The studies retrieved were examined according to the inclusion and exclusion criteria. Time period reviewed was 2000 to 2013. The methodology of skills assessment was examined.

RESULTS: Five hundred and fifteen articles focussed upon simulator based skills assessment. Fifty-two articles were identified that dealt with technical skills assessment in general surgery. Five articles assessed open skills, 37 assessed laparoscopic skills, 4 articles assessed both open and laparoscopic skills and 6 assessed endoscopic skills. Only 12 articles were found to be integrating simulators in the surgical training curricula. Observational assessment tools, in the form of Objective Structured Assessment of Technical Skills (OSATS) dominated the literature.

CONCLUSION: Observational tools such as OSATS remain the top assessment instrument in surgical training especially in open technical skills. Unlike the aviation industry, simulation based assessment has only now begun to cross the threshold of incorporation into mainstream skills training. Over the next decade we expect the promise of simulator-based training to finally take flight and begin an exciting voyage of discovery for surgical trainees.

Key words: Simulation; Surgical training; Surgery; Training; Objective Structured Assessment of Technical Skills; Observational tool; Surgical skills; Assessment; Skill assessment

Core tip: The nature of surgical training has teetered on the brink of a seismic change in how we can deliver the level of expertise required of a modern surgeon for over a decade. It is evolving from Halstedian's apprenticeship model towards simulation-based training similar to the aviation industry. Since 2000 there have been approximately 173 studies about validation of simulators as assessment tools. As the technology grows, its translation into real changes in curriculum is still unclear. This review is focused upon where we currently stand in relation to the effective integration of simulation-based skills assessment into modern surgical training curricula.

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INTRODUCTION

The nature of surgical training has teetered on the brink

of a seismic change in how we can deliver the level of surgical training required of a modern surgeon for over a decade. The demands imposed by a zero complication ethos expected by patients and emphasised by the media has challenged us as surgical educators to continually assess our training paradigms. Traditionally, surgical training has been largely an opportunity-based learning approach based upon an apprenticeship in the operating room (OR). This Halstedian method[1] of surgical training is often exemplified as the "see one, do one, teach one" approach to training. This system which was reliant upon opportunistic encounters particularly of the complex case mix variety remains extremely time dependant. This apprenticeship model resulted in surgical training often being prolonged in order to gain sufficient surgical experience to reach a subjective level of operative experience. In the modern era of surgical training, trainees are continually restricted on the number of hours they can legally work. This may be as low as 48 h per week in Europe[2] or 80 h in North America[3]. These mandated reductions in working hours have been based upon safe guarding both patients and doctors alike in order to decrease potential errors in the health care system. This decrease in hours however will result in a fundamental reduction in the trainees' opportunity for surgical operating time exposure with "real" patients. As a direct consequence of these challenges, interest in laboratories with formal curricula, specifically designed to teach surgical skills, has increased dramatically[4].

The use of surgical simulators and inanimate bench models for training and assessment has been the centre of attraction among the training bodies around the world for well over a decade. The use of simulation for clinical skills training, assessment and clinical scenario management provides educators the freedom of focused training in more controlled environment without risking the life of any patients. Trainees may also have the chance to practice the skills required of a modern surgeon to proficiency at their own pace. The greatest advantage of virtual reality medical simulation is the opportunity to try and fail without consequence for the patient[5]. The integration of simulation into training programmes would therefore seem the next most intuitive step for the design and implementation of any modern surgical training curriculum.

In tandem with the continued development of surgical skills in training surgeons of equal importance is our ability to assess the candidates' proficiency in the performance of these very surgical skills that we have taught. Once again the assessment of surgical skills has been largely subjective and onto this horizon surgical simulation may also provide a solution. The objective characterisation of technical skills can be difficult. Technical performance assessment ranges from basic surgical skills such as knot tying and suturing, basic laparoscopic skills and endoscopy to a wide spectrum of evaluations that include performing complex procedures such as laparoscopic cholecystectomy, vessel anastomosis and tendon repair. Assessment can be defined as making a judgement against a predefined reference[6]. As surgical educators, it is important to assess trainees on their progress in surgical skills in order to ensure that they remain safe in the stressful environment of a real operating theatre. It allows the trainers to give a constructive feedback based on their performances and can be used for the award of certification or even credentialing. Despite its importance to surgeons, technical proficiency historically has been poorly evaluated[7]. A good assessment tool must possess reliability, validity, educational impact, acceptability and feasibility[8].

The aim of this review is to determine where we currently stand in relation to the use of simulation in surgical skills assessment within current training curricula. We focused upon the use of simulators in surgical curricula that embraced the concept of creating proficiency profiles using simulators. Technical performance assessment in laparoscopy, endoscopy and open surgical skills were included.

MATERIALS AND METHODS

This review encompassed a literature search in PubMed from January 2000 to November 2013. The keywords used to search the database were "simulation", "skills assessment" and "surgery". All search result titles and abstracts were reviewed by the authors, SS and PN. Full texts of compatible articles were examined for eligibility of inclusion as agreed by the two authors.

Inclusion criteria

Studies were included if simulators were used in laparoscopic and endoscopic skills assessment following an intervention such as skills training, courses, surgical curriculum and selection process. Also, studies using simulators to assess open technical skills such as knot tying, suturing or a basic open procedure, for example excisions of sebaceous cyst were included.

Exclusion criteria

The review was focused upon the use of simulators in assessment of surgical skills. Studies that aimed at validating their latest simulator alone were excluded. Studies were excluded if the surgical skills are of specific subspecialties such as ophthalmology, urology, gynaecology, cardiothoracic, ear, nose and throat (ENT), neurosurgery, trauma and orthopaedics, as well as non-validated methods, non-technical skills for example cognitive analysis and patient care simulation. Any non-English articles, reviews, conference abstracts, editorial, comments, supplements and case reports were excluded.

RESULTS

The keyword search yielded 515 articles, of which 201 articles were eligible. Following the application of our inclusion and exclusion criteria, there were 52 articles

Table 1 Study characteristics assessing open surgical skills (n = 5)

Ref.	Year	No. of trainees	Tasks	Assessment tool
Acton *et al*[9]	2010	157 clerkship	Suturing	OSATS
Brydges *et al*[10]	2008	38 trainees	One-handed knot tying	Motion analysis (ROVIMAS) and GRS
Chipman *et al*[11]	2009	24 trainees PGY 1	Excision of skin lesion and wound closure	OSATS
Jensen *et al*[12]	2008	45 PGY 1-2	Excision of skin lesion and bowel anastomosis	Video-based OSATS and FPA (wound closure aesthetic quality and anastomotic leak pressure)
Olson *et al*[13]	2012	11 intern	Open laparotomy and bowel anastomosis	OSATS and survey

OSATS: Objective Structured Assessment of Technical Skills; ROVIMAS: RObotics VIdeo and Motion Assessment Software; GRS: Global Rating Score; FPA: Final product analysis.

remained that dealt with technical skills assessment in general surgery. These selected articles were divided into 4 categories according to the skills assessed; open skills (Table 1), laparoscopic skill (Table 2), combination of open and laparoscopic skills (Table 3), and endoscopic skills (Table 4). Out of these articles only 12 studies integrated simulators in a surgical curriculum with technical skills being assessed (Table 5). Only 1 study was found using simulators in the selection process into surgical training programme.

With an increasing emphasis of surgical procedures being undertaken in a minimally invasive approach, it is not unsurprising that the assessment of laparoscopic skills dominate the articles included. This bias is also a result of the reality that laparoscopic skills assessment in a simulator has proved far easier than the assessment of open surgical skills. However, observational-type assessment tools remain the instrument of choice in all the skills, especially when assessing trainees in a real operating theatre (OR).

In the studies identified, 21 employed observational tools, mainly Objective Structured Assessment of Technical Skills (OSATS) as the main scoring system to evaluate their candidates' technical skills performances in open and laparoscopic skills.

The use of simulators in the assessment of laparoscopic skills was evident in 23 publications. Nineteen studies utilised the objective metrics generated by the simulator only and 3 studies used FLS scoring system. One study[17] combined the objective metrics from the simulator with error or injury scores. A total of 13 studies that assessed laparoscopic skills in simulators were using OSATS or checklist-based tools, solely. Out of these, 2 studies[43,45] assessed trainees in the operating theatre (OR) using video-based observational tools following simulation-based training. Interestingly one study[39] combined the performance score on simulator with performance in the OR. Five studies[14,36,37,48,50] used ICSAD combined with other assessment tools or simulator-generated metrics in both open and laparoscopy.

Table 5 outlines reports that incorporated simulators as part of the course in their curriculum. Two of them were for open surgical skills, 6 studies were for laparoscopic skills, 3 studies were for both open and laparoscopic skills and only 1 for endoscopic skills assessment.

One study[40] used virtual reality laparoscopy simulator to assess general surgical applicants who were shortlisted for the residency interview. However, the scores were not used in ranking the candidates for acceptance into the training programme.

DISCUSSION

Simulation in surgery has been a hot topic among surgical educators for more than a decade. In the early millennium, there was an avalanche of studies using simulators that focused on validating the simulators and proving their reliability and fidelity. Since the year 2000 approximately 173 studies were published that specifically reported construct validity of a wide spectrum of surgical simulators. Many new technologies evolved to progressively improve the existing simulators to higher fidelity systems. However despite the plethora of validation studies being completed over a decade ago there is a glaring hiatus in the literature when one examines the results of the integration of these simulators into surgical training curricula. In particular, there is a lack of study showing the implementation of these simulators in the surgical training institutions across the globe, especially in the arena of surgical skills assessment for credentialing. From our review only 12 studies could be identified from the five hundred triaged that have integrated simulation into a surgical training curriculum. There were 52 studies that used simulators in surgical skills assessment within general surgery. The size of these studies was quite modest with 34 having less than 40 candidates and only 5 having greater than 100 candidates.

The main purpose of having simulators in the surgical training arena is for the acquisition of technical skills appropriate to the level of training. This may be undertaken in a safe training environment both from the trainees and patients' viewpoint. Simulation-based surgical training is important in teaching the surgical trainees and to monitor their progress along the training programmes until they possess the essential technical skills without risking patients' lives. In order to grasp this, continuous training and assessment is paramount. Traditionally, trainees' surgical skills are being assessed by examining the logbook and supervisor feedback after certain amount of time in the service. However it is clear that a logbook records experience and is not a marker of expertise[61]. It contains the number of procedures and supervision code, rather than

Table 2 Study characteristics of studies assessing laparoscopic skills (n = 37)

Ref.	Year	No. of participants	Tasks	Assessment tool
Aggarwal *et al*[14]	2007	20 trainees	Laparoscopic cholecystectomy	Motion analysis and video-based GRS
Arora *et al*[15]	2011	25 surgeons	Laparoscopic cholecystectomy	OSATS
Bennett *et al*[16]	2011	70 students	Camera navigation	Box trainer
Botden *et al*[17]	2009	18 students	Laparoscopic suturing	ProMIS™, FPA using 5-point Likert Scale
Buzink *et al*[18]	2012	25 trainees 6 experts	Diagnostic laparoscopy, laparoscopic cholecystectomy and laparoscopic appendicectomy	LapMentor
Cope *et al*[19]	2008	22 interns	6 tasks on MIST VR	MIST VR
Crochet *et al*[20]	2011	26 trainees	Laparoscopic cholecystectomy	VR Simulator
Ganai *et al*[21]	2007	19 students	Angled telescope navigation	VR Simulator
Grantchar-ov *et al*[22]	2009	37 residents	Basic laparoscopic task	MIST VR
Heinrich *et al*[23]	2007	17 experts	26 modules	LapMentor, LapSim, ProMIS™, Surgical SIM
Kanumuri *et al*[24]	2008	16 students	Laparoscopic suturing and knot tying	Video-based performance assessment tool on live porcine
Kolozsvari *et al*[25]	2012	63 residents	FLS tasks[1]	FLS scoring system
Kurashima *et al*[26]	2013	17 residents	Laparoscopic inguinal hernia repair	GOALS-GH
Langelotz *et al*[27]	2005	150 surgeons	Navigation, coordination, grasping, cutting and clipping	VR simulators
LeBlanc *et al*[28]	2010	29 surgeons	Laparoscopic sigmoid colectomy	ProMIS™ simulator, OSATS and operative error
Lehmann *et al*[29]	2012	36 surgeons	2 LapSim tasks	LapSim
Lehmann *et al*[30]	2013	105 surgeons	Lifting and Grasping, Fine dissection	LapSim
Loukas *et al*[31]	2011	25 trainees	Adhesiolysis, bowel suturing, laparoscopic cholecystectomy	LapVR
Loukas *et al*[32]	2011	20 trainees	Adhesiolysis, bowel suturing, laparoscopic cholecystectomy	LapVR
Loukas *et al*[33]	2012	44 novices	Peg transfer, cutting, knot tying	LapVR and video trainer
Lucas *et al*[34]	2008	32 students	Laparoscopic cholecystectomy	OSATS
Mansour *et al*[35]	2012	48 trainees	Peg transfer, clipping	VR simulators
Munz *et al*[36]	2007	20 novices	Intracorporeal knot tying	ICSAD and checklist
Munz *et al*[37]	2004	24 novices	Cutting a shape on a glove and clipping a rubber tube	Motion analysis and error score
Palter *et al*[38]	2012	25 residents	Laparoscopic right colectomy (live and simulator)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim
Palter *et al*[39]	2013	20 trainees	Clipping, and lifting and grasping, laparoscopic cholecystectomy (actual OR)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim
Panait *et al*[40]	2011	42 applicants	Navigation, coordination, grasping, cutting and clipping	LapSim
Rinewalt *et al*[41]	2012	20 residents	FLS tasks	GOALS
Rosenthal *et al*[42]	2006	20 students	Clip and cut cystic duct	Xitact LS500 Virtual Patient
Seymour *et al*[43]	2002	16 trainees	Laparoscopic cholecystectomy (OR)	Video-based operative error scoring system
Sharma *et al*[44]	2013	19 trainees	Laparoscopic cholecystectomy	LAP MentorTM
Stefanidis *et al*[45]	2013	42 novices	Laparoscopic suturing (OR)	GOALS, speed, accuracy and inadvertent injuries
Stelzer *et al*[46]	2009	23 interns	Peg transfer, intracorporeal knot tying in dry lab, running the bowel, intracorporeal knot tying in live porcine model	MISTELS scoring system Video-based modified GOALS
Tanoue *et al*[47]	2010	194 surgeons	Lifting and grasping	LapSim
Torkington *et al*[48]	2001	13 trainees	MIST VR tasks	ICSAD and MIST VR
van Rijssen *et al*[49]	2012	162 trainees	Intracorporeal knot tying	OSATS and Motion Analysis Parameter (MAP)
Varas *et al*[50]	2012	25 residents	Laparoscopic jejunojejunostomy	OSATS, ICSAD, FPA

[1]FLS tasks are peg transfer, pattern cut, endoloop placement, suture with an extracorporeal knot and suture with an intracorporeal knot. GRS: Global rating scale; OSATS: Objective Structured Assessment of Technical Skills; FPA: Final product analysis; MIST-VR: Minimally invasive surgical trainer-virtual reality; VR: Virtual reality; FLS: Fundamentals of laparoscopic surgery; GOALS: Global operative assessment of laparoscopic skills; GOALS-GH: Global Operative Assessment of Laparoscopic Skills-Groin Hernia; OR: Operating theatre; MISTELS: The McGill Inanimate System for Training and Evaluation of Laparoscopic Skills; ICSAD: Imperial College Surgical Assessment Device.

performance scores for a particular procedure. Therefore, logbooks lack content validity[62]. Supervisor feedback assesses the overall performance of a particular trainee and is not exclusively on the technical skills. It is largely subjective and influenced by multiple factors such as patients' condition, theatre environment and hospital condition. Therefore, the need for a more robust assessment tool which is objective, reliable and feasible[63] remains.

In our institution surgical simulators are used as part of the initial selection process and thereafter for skills assessment and ongoing training. Irish surgical trainees are required to attend simulation-based operative skills classes throughout their training programme. Apart from the didactic teachings, practical sessions are provided which

Table 3 Study characteristics of studies in assessment of open and laparoscopic skills (*n* = 4)

Ref.	Year	Number of participants	Tasks	Assessment tool
Beard *et al*[51]	2011	85 trainees	Mixed tasks (OR)	Procedure-based assessment, OSATS
Fernandez *et al*[52]	2012	30 PGY 1	Knot-tying, suturing, laparoscopic skills	OSATS, computer metric-based performance assessments
Mittal *et al*[53]	2012	60 residents	Basic skills(knot tying,wound closure, enterotomy,vascular anastomosis) and FLS	OSATS and FLS
Parent *et al*[54]	2010	28 interns	Wound closure and FLS tasks	Essential item checklist, economy of time, global competence, FLS system

OR: Operating theatre; OSATS: Objective Structured assessment of technical skills; FLS: Fundamentals of laparoscopic surgery.

Table 4 Characteristics of studies in assessment of endoscopic skills (*n* = 6)

Ref.	Year	Number of participants	Tasks	Assessment tool
Ende *et al*[55]	2012	28 residents	OGD	Simulator and observation
Götzberger *et al*[56]	2011	13 trainees	No mention in abstract	Simulator (5-point Likert scale)
Haycock *et al*[57]	2010	36 trainees	Colonoscopy (simulator and OR)	Direct Observation of Procedural Skills and Global Scores sheet
Haycock *et al*[58]	2009	28 trainees	Polypectomy, control of upper GI bleeding and oesophageal dilation and PEG insertion	Station-specific checklist and global score
Shirai *et al*[59]	2008	20 residents	OGD	11 items 5-grade scale
Van Sickle *et al*[60]	2011	41 trainees	Colonoscopy	GI Mentor Ⅱ and GAGES

OGD: Oesophago-gastro-duodenoscopy; GI: Gastrointestinal; PEG: Percutaneous Endoscopic Gastroscopy; GAGES: Global Assessment of Gastrointestinal Endoscopic Skills.

allow the trainees to practice their skills in open surgery, laparoscopy and endoscopy. Basic surgical trainees are assessed at the end of their training years. Trainees who underperform are required to attend a remedial day where their performances will be discussed with the faculty. For the past 6 years, all candidates shortlisted for Higher Surgical Training (HST) programme in general surgery, cardiothoracic and plastic surgery are required to go through surgical skills assessments prior to their interviews. Their scores carry 10% marks in their overall markings. Gallagher *et al*[64] showed that four out of five top performers on technical skills stations during selection of higher surgical trainee in general surgery were in the top-ranked applicants overall and subsequently succeeded in being selected into the HST programme. In plastic surgery, Carroll *et al*[65] proved those applicants selected for HST performed better in all six tasks (laceration repair, Z-plasty, lipoma excision, sebaceous cyst excision, tendon repair and arterial anastomosis) than those who were not.

OSATS remains the selected assessment tool of choice in the evaluation of surgical skills. In our own training programme it is used for all open surgical procedures with inanimate bench models such as bowel anastomosis, excision of lipoma or sebaceous cyst and laparotomy incision and closure. Each station is assessed by an expert surgeon relative to the specialty and all stations are run simultaneously within a time frame. For laparoscopic skills, OSATS assessment is combined with performance on ProMIS™ laparoscopic simulator (Haptica, Dublin, Ireland). The tasks for laparoscopic skills generally include object positioning and sharp dissection. Promis™ simulators score the trainees or candidates according to the total path length, smoothness, time and error. In general surgery and cardiothoracic skills assessment, the GI Mentor endoscopy simulator (Simbionix, Cleveland, OH, United States) and a 15-item checklist are used to assess candidates' endoscopic skills. GI Mentor could provide time and the percentage of mucosa visualised as objective score in the assessment.

From this review, we identified that the main instruments utilised in practice remain observational tools for both open and laparoscopy. This is despite a myriad of validated computer-based simulators being available in laparoscopy. The most commonly used observational tool is the Objective Structured Assessment of Technical Skills or OSATS. It consists of 2 sets of evaluation checklist; operation-specific checklist and global rating scales. It is consistent with the format of the typical Objective Structured Clinical Examination (OSCE) in which examinees perform a series of clinical tasks at each of several time-limited stations[66]. In another study[41], a different type of observer-dependant assessment tool was used for assessing laparoscopic skills called Global Operative Assessment of Laparoscopic Skills (GOALS). It was developed by a group of researchers[67] in Quebec, Canada. This consists of a checklist and 2 visual analogue scales (VAS). All these observational tools require a minimum of two independent assessors in order to avoid bias in scoring the candidates by single assessor. Therefore, a group of expert surgeons should be recruited to use these assessment tools. This could be done either live during the assessment or by video recordings. Since

Table 5 Characteristics of studies integrating skills assessment tools in a simulation-based curricula and selection process (n = 12)

Ref.	Year	No. of participants	Tasks	Assessment tool
Open skills				
Chipman *et al*[11]	2009	24 trainees	Excision of skin lesion and wound closure	OSATS
Olson *et al*[13]	2012	11 interns	Open laparotomy, bowel anastomosis	OSATS and survey
Laparoscopic skills				
Buzink *et al*[18]	2012	25 trainees 6 experts	Diagnostic laparoscopy, laparoscopic cholecystectomy and laparoscopic appendicectomy	LapMentor
Palter *et al*[39]	2013	20 trainees	Clipping, and lifting and grasping, Laparoscopic cholecystectomy (actual OR)	Video-based procedure-specific evaluation tool, modified OSATS global rating scale and LapSim tasks
Panait *et al*[40]	2011	42 applicants	Navigation, coordination, grasping, cutting and clipping	LapSim
Rinewalt *et al*[41]	2012	20 residents	FLS tasks	GOALS
van Rijssen *et al*[49]	2012	162 trainees	Intracorporeal knot tying	OSATS and Motion Analysis Parameter(MAP)
Varas *et al*[50]	2012	25 residents	Laparoscopic jejunojejunostomy	OSATS, ICSAD, FPA
Open and laparoscopic skills				
Fernandez *et al*[52]	2012	30 PGY 1	Knot-tying, suturing, laparoscopic skills	OSATS, computer metric-based performance assessments
Mittal *et al*[53]	2012	60 residents	Basic skills(knot tying,wound closure, enterotomy, vascular anastomosis), FLS tasks[1]	OSATS and FLS score
Parent *et al*[54]	2010	28 interns	Wound closure, FLS tasks[1]	essential item checklist, economy of time, global competence, FLS score
Endoscopic skills				
Van Sickle *et al*[60]	2011	41 trainees	Colonoscopy	GI Mentor Ⅱ and GAGES

[1]FLS tasks are peg transfer, pattern cut, endoloop placement, suture with an extracorporeal knot and suture with an intracorporeal knot. OSATS: Objective Structured Assessment of Technical Skills; FLS: Fundamentals of Laparoscopic Surgery; GOALS: Global Operative Assessment of Laparoscopic Skills; ICSAD: Imperial College Surgical Assessment Device; FPA: Final Product Analysis.

multiple assessors are required to make these tools valuable, there should be a minimum discrepancy between the scores among the assessors. Otherwise, the scores can be open to critique. In order to prove the degree of agreement among the assessors, inter-rater (IR) reliability is used. IR value should be at 0.8, which means the assessors are in agreement in 80% of the scores but in disagreement in the rest of 20%. A high value of IR reliability indicates that the scores are homogenous and the assessment tool is both robust and of value. In one of the study[13], IR reliability was 0.67 which reflects significant differences of opinion of assessors in the subjective data they are evaluating. This emphasises the weakness of this scoring system, as well as the labour intensive nature of the scoring system. In all these studies the candidates could feel appropriately aggrieved if the arbitrators of success in any task undertaken demonstrated significant difference in opinion as evidenced by such a low IR reliability score. We would contend that the use of a truly objective assessment *via* simulation in real time must inherently be a stronger approach to assessment.

As with every technology there are a variety of simulators available on the market that has been used in surgical skills assessment. In laparoscopic training and assessment, computer-based simulators are able to provide objective metrics after completion of a laparoscopic task. Some examples of validated virtual reality (VR) simulators available in laparoscopy are MIST VR, LapSim, LapMentor and Xitact LS500[68]. These simulators are able to assess various laparoscopic skills such as camera navigation, object positioning and manipulation, intracorporeal suturing and sharp dissection. However, the main criticism on VR simulators is that they lack of real life representation such as delayed gravity effect and no haptic feedback, as found in LapSim[36].

A hybrid simulator, ProMIS^{TM} (Haptica, Dublin) used 100% VR for certain tasks and augmented reality that overlays graphics onto a task performed on a physical exercise[69]. It provided the tactile feedback which is lacking in most VR simulators. VR and hybrid simulators are able to quantify skills in terms of path length, smoothness, economy of movement and time. The simulators also are able to identify the errors performed specific to the procedures and include them in the final report. Various studies have shown their validity and reliability[70-76]. However, these simulators are largely used for learning and practising the skills but rarely used as an assessment tool. Only 56% of the studies in this review employed simulator-generated objective metrics in the laparoscopic skills assessment, either exclusively or combined with other assessment tools.

Endoscopic skills also can be trained and assessed using simulators. Training in endoscopy in a virtual environment is thought to be a good alternative to classical bedside teaching, but without its adverse effects, such as patient discomfort, risk of perforation, and longer examination time[77]. GI Mentor (Symbionix, Israel) is one of the commonest endoscopy simulators used in surgical training institution. After the performance of a case on the simulator, the trainee is presented with an evaluation of performance such as time taken, percentage of mucosa visualized, and percentage of time spent without

clear vision (red-out)[78]. Recently, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) developed Fundamental of Endoscopic Surgery™ (FES™) as a training and assessment tool for basic skills in endoscopy[79].

There are fundamental differences in the skills required for laparoscopic surgery as compared to open surgery[80]. Without doubt it is clear from the literature that the use of simulators in open surgery represents a challenge. In general the progression of simulator development has tended to target minimally invasive surgery (MIS)[75]. Nonetheless, open surgery remains to be the paramount procedures across surgical specialties. It is vital to teach surgical trainees and assess their skills in open surgery during their training years. Inanimate bench models such as the laparotomy model from Simulab Corporation (Seattle, WA), skin pads and saphenofemoral junction model from Limbs and Things (Bristol, United Kingdom) are amongst most commonly used in training and assessment. Animal models, either cadaveric or live, have been used in some studies but plagued by ethical issues in regards to animal rights. In United Kingdom, the use of live animals is not permitted under the current law, unlike in Europe, United States and other countries[81]. Martin *et al*[82] showed bench top simulations gave equivalent results to the use of live animals.

The challenge for the assessment of open surgical skills is to decide what parameters should be evaluated. The role of simulators in the assessment of open surgery however may lie in the determination of a surgeon's dexterity. The objective measurement of a surgeon's technical skill or level of dexterity has proved to be very difficult. Surprisingly only 1 study combined OSATS with motion analysis system in an attempt to capture the essence of dexterity[10]. The technology behind the measurement of dexterity in surgery and in particular open surgery is however slowly evolving. The researchers in Imperial College London developed a motion tracking system called Imperial College Surgical Assessment Device (ICSAD). This is a combination of a commercially available electromagnetic tracking system (Isotrak Ⅱ, Polhemus Inc,Colchester, VT) and bespoke computer software program[83]. It measures the time taken, path length and number of movements in open and laparoscopy skills assessment. This has been shown that the measurements were able to discriminate different level of surgical experience in laparoscopy[48] and open surgical procedures[84]. Then, RObotics VIdeo and Motion Assessment Software (ROVIMAS) replaced the former ICSAD motion analysis software and integrated an improved version of data acquisition module including real-time synchronized motion-video capture functionality[85]. Despite these technologies being now over a decade old it remains largely a research tool rather than incorporated into main stream curricula.

The measurement of dexterity alone is insufficient without it being in the appropriate context. In essence, dexterity may be independent of the quality of the end result: This represents surgical context. Errors such as slip knot and incorrect suture placement could cause horrendous morbidity towards patients. It is the appreciation of these errors that underpins the concept of placing skills assessment and the associated metrics in the correct context.

The majority of assessing errors or analysing the end product is observational. A crude assessment of the quality of the final product is by using a 5-point scale[86]. Scott *et al*[87] formulated a proficiency score which include a series of errors observed for knot tying and suturing skills and maximum allowable task duration as cutoff time. The formula used was as follow: Score = (cutoff time) - (completion time) - 10 (sum of errors); a higher score indicates superior performance[86]. A significant weight was given to the sum of errors showing the importance of the end-product quality in surgical skills assessment. Patel *et al*[88] developed low-fidelity exercises for basic skills training and assessment and proved its validity. The exercises were needle driving, knot tying, two-hand coordination and fine motor coordination. The metrics measured include time, accuracy and number of targets completed for needle driving exercise or number of appropriate knots for knot tying exercise. Again, this is open to bias and labour intensive. In practice, the quality of knots is easily tested by spreading the loop until they are either break or slip. However, this is hardly performed with a standardised force by surgical educators. Several studies have used tensiometers to assess the quality of the knots[89-92]. Brydges *et al*[93] developed a measurement for wound closure skill performance called 'absolute symmetry error', which measure related to the "bite size" on each suture placement. It does not require an expert assessor and feasible for self-training and assessment. A few studies assessed the end product of bowel anastomosis by measuring the leak pressure[12,50]. These studies combined the validated assessment tool with final product analysis (FPA). By combining these components in the assessment of skills, trainees' appraisal is thought to be more accurate and apparent. From our review of the literature, only 2 studies[17,28] combined virtual reality simulator generating metrics combined with error scoring systems in their assessments. This approach would seem sensible when one is considering surgical skills assessment.

There is a vast quantity of published data available underpinning the validity of surgical simulators. However, it was abundantly evident from our review that only a small number of papers have outlined their use as part of a training curriculum. It should be noted that the literature search was restricted to English language publications only. In total, twelve studies were identified that incorporated simulation-based training in the curriculum. The participants in these studies went through various periods of time in training using simulators and their performances in technical skills were assessed at the end of the training phase. OSATS or other observational tools were used to assess open skills in 5 studies. For

laparoscopic skills, only 2 of these articles used simulators alone in the assessment and 3 studies combined the simulator score with observational assessment tools. Only 1 study[50] assessed trainees' performances using multimodal assessment tools which were OSATS, ICSAD and final product analysis (FPA) (leakage and permeability of an anastomosis). In another study[60], endoscopic skills were assessed by a combination of the simulator-based scores and Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) scores. Two studies developed intensive boot camp session for new residents in order to boost their basic technical skills at the start of their training programme[52,54]. Both studies assessed open technical skills using observational tools and for laparoscopic skills, one study[52] used computer-generated metrics and the other study[54] used FLS scoring system. Fernandez *et al*[52] proved that the new residents' performances improved after the 9-wk intensive course. However, in the other study[54] the boot camp course ran for only 3 d and the performances did not show any significant difference compared to the control group. Interestingly, only 1 study[38] assessed trainees performances in a simulation lab and thereafter in OR. After training to proficiency with the simulators, the trainees were required to perform laparoscopic cholecystectomy with their supervisors and the performances were video-recorded. These recordings were then assessed using observational tools. This was the only study that seemed to report active integration of simulator based surgical skill training and translation into real time clinical practice.

It is clear that the assessment of surgical skills in simulation laboratories is robust. The critical question is whether the skills acquired from simulation-based curriculum are transferrable to real operations. The most recent systematic review by Buckley *et al*[94] demonstrated that simulation-based training has a positive impact on operative time and predefined performance scores in the OR but not the quantifiable measures such as ergonomics, hand dominance and smoothness of movement as measured by simulators. The fundamental assumption of simulation-based training is that the skills acquired in simulated settings are directly transferable to the operative setting[95]. If this assumption is proven to be true, simulation-based curriculum must be one of the main pillars in creating top-quality surgeons which in turn would guarantee an excellent patient care and safety.

Over the last decade, observational assessment tools, such as OSATS, remain the most used methodology to assess surgical skills. It has been over a decade since motion tracking systems were reported as effective tracking tools in assessing surgical skills[96]. Despite the advancement in simulation technology, this available technology has not been fully incorporated into surgical training curricula. This is particularly true for the assessment of open skills. One must therefore query why this is the case. We initially had a frenzy of validation studies since the turn of the millennium in relation to simulators. Following this, technology has only improved in terms of fidelity and reproducibility. The dearth of information in the literature regarding the efficacy of the use of simulators in training programmes may be related to the paucity of data on translating simulator based training into the real patient setting. Yet the conversion from VR to OR as coined by Professor Anthony Gallagher[97] perhaps is finally beginning to get traction. In the past 14 years there have been 12 articles that report their experience of simulators within their general surgical training programmes. One of these has now translated this VR training into OR in practice.

The integration of surgical skills assessment as part of the selection process for Higher Surgical Training (HST) selection in the Irish National Training Programme is a further example of the potential that simulation holds for the surgical training community. One can only hope that over the next decade, now that the validity of simulator based training has finally being accepted, the future of simulation-based surgical training will no longer stand on the precipice but finally take flight.

COMMENTS

Background

The traditional apprenticeship model for surgical training as described by William Halstead is reliant on opportunity in order to gain sufficient surgical skills. In the current climate, surgical training is focusing on integrating simulators in the formal curricula, including surgical skills assessment of the trainees.

Research frontiers

For the past 14 years, there is a plethora of published studies that involved validation of various simulators. However, the integration of these simulators in surgical skills assessment as an objective measurement is still minimal.

Innovations and breakthroughs

The authors identified that observer-dependant tool remains largely a tool of choice when assessing both laparoscopy and open technical skills. Some of the studies outlined the use of simulators in objective assessment of laparoscopic skills and minimum amount of studies showed the application of non-observer dependant tool in the assessment of endoscopic and open surgical skills.

Applications

The assessment of surgical skills using simulators is highly applicable in surgical curriculum. The next step is to engage the simulation technology in the assessment of technical skills in a real operative setting.

Terminology

Observational tool: Checklist-based assessment tool used by surgical experts; OSATS: Objective Structured Assessment of Technical Skills.

Peer review

This is a very nice review of the available literature on the results of simulation training on surgical residents.

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CASE REPORT

Cyanoacrylate spray as treatment in difficult-to-manage gastrointestinal bleeding

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Abstract

Gastrointestinal bleeding can be a life-treating event that is managed with standard endoscopic therapy in the majority of cases. However, up to 5%-10% of patients may have persistent bleeding that does not respond to conventional measures. Several endoscopic treatment techniques have been proposed as strategies to control such cases, such as epinephrine injection, hemoclips or argon plasma coagulation, but there are certain clinical scenarios where it is difficult to achieve hemostasis even though adequate use of the available resources is made. Reasons for these failures can be associated with the lesion features, such as extent or location. The use of long-standing techniques in non-traditional scenarios, such as with cyanoacrylate for gastric varices sclerosis, has been reported with favorable results. Although new products such as TC-325 or Ankaferd Blood Stopper hemosprays may be useful, their formulations are not available worldwide. Here we present two clinical cases with very different scenarios of gastrointestinal bleeding, where the use of cyanoacrylate in spray had favorable results in uncommon indications. Cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings.

Key words: Cyanoacrylate; Gastrointestinal bleeding; Hemostasis; Mexico; Spray

Core tip: Up to 5%-10% of patients with gastrointestinal bleeding may have persistent bleeding that does not respond to endoscopic measures. When failure of the initial management strategy is observed, new techniques can be used. Cyanoacrylate is a polymer that crystallizes upon contact with blood and, if used as a spray, can help achieve hemostasis with minimal or no risk to patients.

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INTRODUCTION

Upper gastrointestinal (GI) bleeding is a common disease, with approximately 48% of cases related to peptic ulcer disease[1]. Although endoscopy is highly effective in the control of active bleeding, up to 5%-10% of patients may have persistent bleeding that does not respond to conventional measures, or have recurrent bleeding that is common in conditions in which the underlying disease is not cured (*e.g.*, varices, tumors)[2]. In this scenario, recurrent bleeding can be considered an independent risk factor potentially leading to mortality[1].

An ideal method of endoscopic hemostasis would

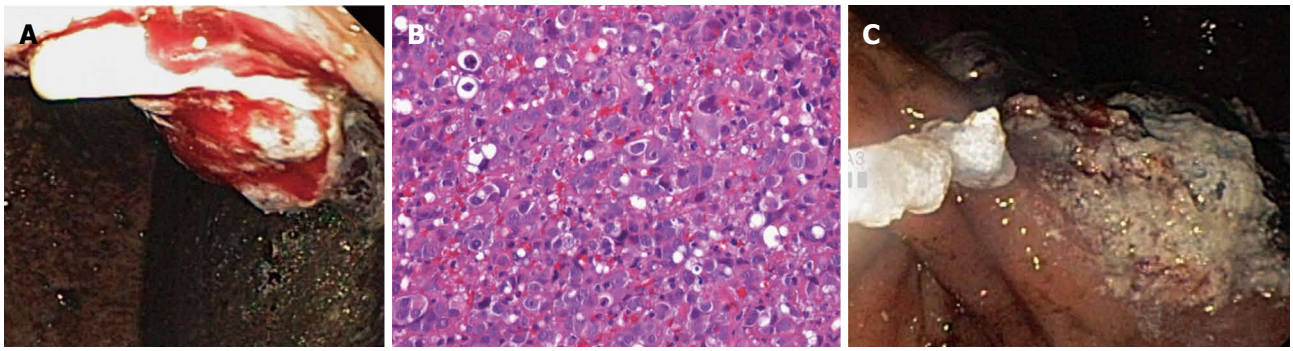

Figure 1 Patient with ulcerated adenocarcinoma of the lower third of the esophagus. A: Ulcerative lesion at the minor curvature with oozing; B: Diffuse adenocarcinoma (poorly differentiated). Neoplastic cells alternate with polymorphonuclear cells; C: Ulcerative lesion after cyanoacrylate spray.

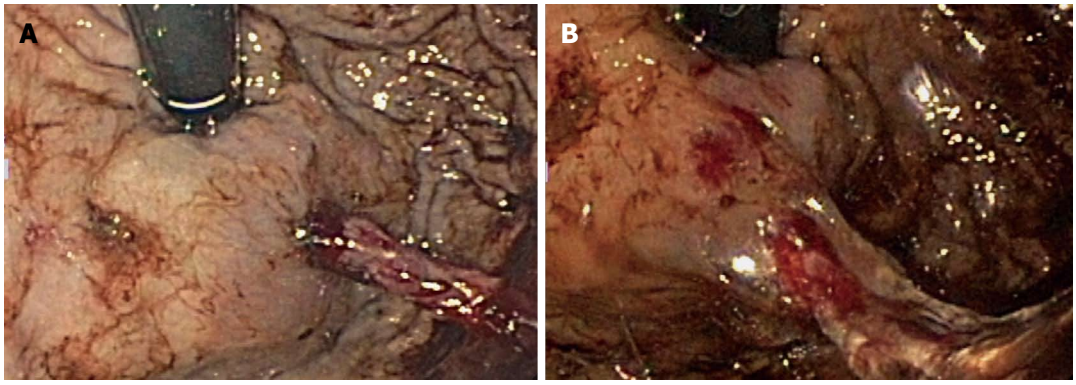

Figure 2 Gastric varices with active bleeding after sclerotherapy with 2-octyl cyanoacrylate. A: Bleeding fundic varices; B: Control of bleeding after placement of cyanoacrylate spray.

immediately stop active bleeding and prevent recurrent bleeding in both the short- and long-term for all types of lesions, be easy to apply to focal and diffuse areas in all locations in the GI tract, cause no significant tissue injury, be safe for the patient, endoscopist, and endoscope, have no limitation regarding the amount of therapy that can be applied, work in patients with decreased thrombotic function, and be inexpensive[3]. Currently, no endoscopic therapy achieves all of these characteristics, so new techniques or products must be proposed. Therapeutic measures using cyanoacrylate spray or new formulations, such as dust Hemospray (Cook Medical, Bloomington, IN, United States) have been proposed to achieve hemostasis[4], but the latter is not available worldwide.

We report two clinical cases and their follow-ups demonstrating the usefulness of cyanoacrylate as a spray for GI bleeding.

CASE REPORT

Patients were seen between October 2013 and January 2014 because of GI bleeding and failure of conventional endoscopic techniques. The clinical courses before and after endoscopies were reviewed. Hemostasis was defined as no oozing or spurting at the conclusion of endoscopy. All patients signed a consent form before the procedures.

Spray technique

Using a 23-gauge injection needle catheter positioned 1 cm outside the tip of the endoscope, a total of 0.5-2.0 mL of a mixture of *N*-butyl-2-cyanoacrylate (Histoacryl; B. Braun Medical, Bethlehem, PA, United States) with lipiodol (0.5 mL:0.6 cc) was sprayed directly over the bleeding site, followed by a rapid 5-mL normal saline solution flush. After the spray, the needle was withdrawn inside the catheter, and the entire endoscope was removed, with the tip of the catheter sheath projecting outside the endoscope. The tip of the catheter was cleaned externally and removed.

Case 1

A 62-year-old male patient with a history of ulcerated adenocarcinoma of the lower third of the esophagus received preoperative chemotherapy and a partial gastrectomy and esophagectomy (with resection of the middle and lower third). After surgery, radiochemotherapy was administered and he remained under surveillance.

After three years of follow-up, the patient showed disease recurrence and presented with melena and epigastric and midgut pain. Upper endoscopy was performed, and a malignant ulcer was seen in the lesser curvature, starting from the anastomosis until the pre-pyloric area, and the pathology report indicated an adenocarcinoma

Table 1 Patients included in previous reports on cyanoacrylate spray use

Ref.	Sex/age (yr)	Cause of bleeding	Prior therapy	Glue mixture	Glue volume	Treatment (n)	Outcome	Follow-up
Walia *et al*[8]	F, 89	2 cm ulcer in duodenal bulb	20 mL of epinephrine solution (1:10000) + bipolar cautery and hemoclips	n-butyl-2-cyanoacrylate/ normal saline	4 mL	1	Successful hemostasis	No rebleeding
	M, 40	3 cm posterior duodenal bulb ulcer with arterial spurting	Epinephrine injection and hemoclip	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	1	Hemodynamic parameters stabilized	Prophylactic angiographic embolization
	M, 55	2 cm duodenal bulb ulcer with arterial spurting	4 mL of epinephrine injection and bipolar cautery	n-butyl-2-cyanoacrylate/ normal saline	1 mL	1	Recurrent hematochezia 2 d after procedure	Died 31 d later due to uncontrolled sepsis
	M, 69	Oozing gastric vascular ectasia along the lesser curvature	Argon plasma coagulation and hemoclips	n-butyl-2-cyanoacrylate/ normal saline	1 mL	1	Hemostasis	Recurrent gastrointestinal bleeding 18 d later from vascular ectasia in a different location
	M, 59	Active oozing underneath hemoclip applied after hot snare polypectomy of 1.5 cm rectal polyp	hemoclips	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	1	Hemostasis achieved	No rebleeding
Prachayakul *et al*[6]	M, 84	5 cm gastric cancer at lesser curvature with oozing	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	3.0 mL	1	Hemostasis achieved	No rebleeding at 9 wk
	F, 76	5 cm sessile polyp in the ascending colon with oozing	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	2.0 mL	1	Hemostasis achieved	No rebleeding at 5 wk, patient died
	M, 15	Metastasizing germinoma with duodenal invasion	Epinephrine injection (1:20000)	En/Lip 0.5:0.8 + sterile water	1.0 mL	1	Rebleeding at 48 h, and required angio-embolization	Continues to bleed, patient alive
	M, 56	Pancreatic cancer with gastric invasion (6 cm ulcerating mass with oozing in the upper part of the lesser curvature)	Metallic clip	En/Lip 0.5:0.8 + sterile water	1.0 mL	1	Hemostasis achieved	No rebleeding at 6 wk
	F, 62	Ampullary carcinoma with invasion to the second portion of duodenum	Epinephrine injection (1:20000) Argon plasma Failed embolization	En/Lip 0.5:0.8 + sterile water	1.5 mL	1	Hemostasis achieved	No rebleeding at 9 wk, patient died
Shida *et al*[7]	-	Pancreatic cancer with invasion into intestinal wall	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Gall bladder cancer with invasion into intestinal wall	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Mucosal resection in sigmoid colon	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data
	-	Duodenal ulcer	No data	n-butyl-2-cyanoacrylate/ normal saline	0.5 mL	No data	Hemostasis achieved	No data

En/Lip: Enbucrilate/lipidol.

(Figure 1A and B). Further studies confirmed the diagnosis of stage Ⅳ esophageal adenocarcinoma. Fifteen days later, the patient returned due to two episodes of melena, associated with epigastric and mesogastric pain with hemoglobin 10.1 g/dL. In the upper endoscopy, no specific source was detected and oozing was observed in the entire ulcerated area of the lesser curvature. Histoacryl with lipidol (1 mL total) was sprayed on the surface of the tumor through a 23-G catheter until hemostasis was achieved (Figure 1C). The patient was discharged after 72 h with no evidence of rebleeding. After six weeks of follow-up, the patient was alive with no evidence of recurrence of bleeding.

Case 2

A 48-year-old male patient with a history of type 2 diabetes mellitus, hypertension, Evans Syndrome, chronic renal failure, heart failure (American Heart Association/New York Heart Association class Ⅱ-Ⅲ), and decompensated liver cirrhosis due to hepatitis C virus infection (ascites and recurrent variceal bleeding) was admitted for upper endoscopy. Large esophageal varices were observed along with gastric varices (GOV1). Sclerotherapy of gastric varices was performed with 2-octyl cyanoacrylate, but hemostasis was not achieved, with the presence of persistent bleeding after puncture (Figure 2A). Therefore**,** Histoacryl with lipidol was sprayed on the surface through a 23-G catheter until hemostasis was achieved (Figure 2B). In the follow-up, no recurrent bleeding was documented and the patient was discharged after 72 h. After three months of follow-up, no recurrence of bleeding or adverse effects were reported.

DISCUSSION

We demonstrate favorable results with cyanoacrylate spray application in two different cases of difficult-to-treat GI bleeding. Cyanoacrylate has been intensively studied and has been clinically applied as a tissue adhesive in ear surgery, bone grafts, repair of fistulas and skin closures[5]. Cyanoacrylate is from a class of synthetic rubbers that are used as monomers and polymerize in an exothermic reaction after coming into contact with a weak base such as blood[5]. There are two forms used in endoscopy. Enbucrilate (*N*-butyl 2-cyanoacrylate; Histoacryl) is formed of an alkyl group of four carbons, whereas acrylate (2-octyl cyanoacrylate) has an alkyl group of eight carbons (Dermabond; Johnson and Johnson, New Brunswick, NJ, United States)[5]. Histoacryl has been widely used for digestive bleeding due to gastric varices, and is currently medically approved by the United States Food and Drug Administration. It has several advantageous properties, among which the polymerization upon contact with blood enables its effective use. It is thought that the fluid used to clean the injection needle can influence the polymerization time. For the present cases, a saline solution was used for cleaning the needle at the end of the procedure as it triggers polymerization of the rubber, which does not occur with distilled water. We achieved similar favorable results with this combination as with a previous report by Prachayakul *et al*[6].

The use of cyanoacrylate in a spray is not a standard modality for endoscopic treatment of GI bleeding. Table 1 describes the 14 cases that have been reported. Most of the cases used the technique with only saline reported by Shida *et al*[7], which was used as a rescue therapy in lesions where hemostasis had been difficult to achieve by conventional methods with argon plasma, epinephrine or hemoclips[7]. In these cases, hemostasis was achieved, but there were no data on the follow-up of the patients. Prachayakul *et al*[6] reported the successful use of cyanoacrylate and lipidol in a 0.5:0.8 ratio with sterile water with no adverse effects for treating tumoral lesions[6]. Only one of their patients showed rebleeding during the nine-week follow-up period. In the data presented by Walia *et al*[8], three patients experienced rebleeding in a median follow-up of 42 d (range: 30-120 d)[8]. In our two cases, neither of the patients presented recurrence of bleeding on follow-up.

The importance of this technique is the ease of use and the absence of special equipment required, making it accessible to different institutions and clinical settings. We report the use of this technique in two different clinical settings of GI bleeding with favorable results. There has been concern about the possibility of embolism with intravenous application, but this would not occur with the spray technique. There are reports of new products, such as Hemospray and Ankaferd Blood Stopper (Ankaferd Health Products Ltd., Istanbul, Turkey)[9], but these products are not available worldwide.

In conclusion, cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings for uncontrollable GI bleeding.

COMMENTS

Case characteristics

Two patients with persistent gastrointestinal (GI) bleeding that did not respond to conventional measures of endoscopic treatment.

Clinical diagnosis

One patient with gastric varices and another with ulcerated adenocarcinoma of the lower third of the esophagus.

Treatment

Endoscopic treatment with Histoacryl sprayed directly over the bleeding site was used with good results.

Related reports

Scarce information about cyanoacrylate in spray is reported.

Experiences and lessons

Cyanoacrylate used as a spray is a technique that can be used as an alternative method in emergent settings for uncontrollable GI bleeding.

Peer review

The authors describe the technique of using cyanoacrylate spray for GI bleeding and two successful cases are reported. The article provides a technique that is useful in a clinical background.

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CASE REPORT

Endoscopic retrieval of an 18-cm long chopstick embedded for ten months post-automutilation in the esophagus of a patient with psychosis

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Abstract

Foreign body ingestion is an emergency or acute situation that commonly occurs in children or adults and involves the ingestion of one or more objects. Moreover, once the discovery of swallowed foreign bodies has been made, families are typically very anxious to have the patient see a doctor. If the foreign object becomes embedded in the digestive tract, it must be removed; in emergencies, this is done by endoscopy or surgery. This case report presents the successful endoscopic retrieval of a chopstick with both sides embedded 4 cm into the esophageal wall for > 10 mo in a male patient following automutilation in an attempt to be released from a psychiatric hospital. Hot hemostatic forceps were used to open the distal esophageal mucosa in which the chopstick was embedded. The procedure was performed under intravenous general anesthesia and took approximately 7 h.

Key words: Foreign body; Esophagus; Endoscopy; Chopstick; Gastroscope; Hot hemostatic forceps

Core tip: Foreign body ingestion is an emergency that often occurs in children or adults with psychiatric disorders or mental retardation. Here, we report the unique case of a chopstick lodged in the esophagus for 10 mo in a 50-year-old man. The chopstick was embedded 4 cm into the esophageal wall at both ends. Therefore, the procedure was performed under intravenous anesthesia. We made a 4-cm long incision, approximately 1 cm in depth in the esophageal mucosa using hot hemostatic forceps. This procedure took approximately 7 h to perform and an 18-cm long chopstick was removed.

Li SX, Li H, Chen T, Xu MD. Endoscopic retrieval of an 18-cm long chopstick embedded for ten months post-automutilation in the esophagus of a patient with psychosis. *World J Gastrointest Endosc* 2014; 6(9): 453-456 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i9/453.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i9.453

INTRODUCTION

Ingestion of foreign bodies that lodge in the upper gastrointestinal (GI) tract is a common clinical situation. Most of these objects pass through the GI tract spontaneously, but some require emergency endoscopic or surgical removal. Here, we report the first case of a patient with psychosis who had a chopstick lodged in the esophagus with both ends embedded in the esophageal wall for > 10 mo. The patient had a 2-mo history of repeated fever prior to foreign body removal. Ten months previously, the patient experienced a sudden loss of appetite and displayed repetitive behavior of touching his sternum with his hand. The patient's family brought him food daily. He experienced repeated episodes of emesis and fever for 2

mo before the family brought him to the hospital.

CASE REPORT

Foreign body ingestion is a commonly encountered clinical problem and emergency endoscopy case. The patient had swallowed a chopstick following self-mutilation in an attempt to be released from a psychiatric hospital. He refused to say why he would not take fluids daily until his repeated vomiting and fever gradually exacerbated. The family took him to see a doctor in the GI/Internal Medicine Department of our hospital. Chest computed tomography (CT) revealed the tip of an esophageal foreign body as well as a bilateral lung infection (Figure 1A and B). Gastroscopy revealed a chopstick with both ends lodged 4 cm in the esophagus wall (Figure 1C).

The patient's family chose to have the foreign body removed by gastroscopy rather than by a surgical procedure. Initially, a snare was used to tentatively remove the chopstick, however, this attempt failed (Figure 2A). After that, the bagging around the proximal esophageal mucosa was cut 22 cm from the incisors. However, the esophageal mucosa was fixed, and the field of vision was insufficient. Eventually, the esophageal wall was cut and wrapped on the far side of the chopstick using a hook knife. However, because the esophageal wall mucosa was > 1 cm thick, the hook knife was unable to cut properly. We cut the tissue using hot hemostatic forceps (Figure 2B), the distal end of the chopstick was freed (Figure 2C) and then removed by a snare and foreign body clamp. The full length of the removed chopstick was 18 cm (Figure 2D). The procedure was performed under intravenous anesthesia and took approximately 7 h to perform. On postoperative day 1, the patient experienced sustainable chest pain and had a maximum body temperature of 38.5 ℃. The patient's condition gradually improved, and he was discharged on postoperative day 7.

DISCUSSION

Ingestion of foreign bodies is common in clinical practice[1-3]. However, most foreign body ingestion occurs in children between 6 mo and 6 years of age; the rate of foreign body ingestion in adults is lower[4]. In adults, it occurs more commonly in patients with psychiatric disorders, mental retardation, or impairment caused by alcohol. The vast majority of swallowed foreign bodies are found and removed in a timely manner by endoscopy or surgery. This is the first report of ingestion of a foreign body in a patient with psychosis that remained lodged in the esophagus for > 10 mo. Because patients do not like the psychiatric hospital environment, they attempt self-mutilation in order to go home, according to family members. An 18-cm long chopstick is difficult to swallow and would require an external force to enter the esophagus. The distal end of the chopstick may pierce the esophageal mucosa slightly, but cannot pass through the cardia easily. The esophageal peristaltic wave that occurs while eating may move the chopstick tip in close contact with the esophageal mucosa. Reactive hyperplasia that would subsequently occur could embed the chopstick as a foreign body. In this case, hyperplasia of approximately 4 cm × 2 cm in the esophageal mucosa at both ends of the chopstick was noted after 10 mo.

The type of foreign body may determine the complications. Our patient was first examined to determine whether the chopstick had perforated the esophageal wall; this was suspected as the patient had recurrent fever. The CT results were important, and helped us determine that the chopstick perforated only the hyperplastic tissue and not the esophageal wall.

The type of foreign object differs as well. The commonest types of foreign bodies are endoscopically removed in a reliable and safe manner by skilled endoscopists, with a high success rate[5]. Chopstick removal is associated with a high degree of risk; a skilled endoscopist is needed to perform a preoperative assessment and develop a good treatment plan. Esophageal perforation may require surgical management. We believe that endoscopic removal of foreign bodies is best done in the operating room.

In this case, because both ends of the chopstick were tightly embedded in the esophageal wall membrane, we suggested that the foreign body should be removed surgically, but the family insisted on gastroscopy. We found that this would be possible only if one end of the chopstick could be freed. Initially, we needed to determine if this would be the proximal or distal end. The chopstick was exposed at the distal end, approximately 22 cm from the incisors. Only a slight uplift of the esophageal mucosa was visible, and the mucous membrane was not fixed. Initially, we attempted to cut the esophageal wall which was wrapped around the distal end of the chopstick using a hook knife, but because the esophageal wall membrane was approximately 1 cm thick, the hook knife was not sufficient. We then used hot biopsy forceps to make a vertical incision in the mucosa to free the distal end of the chopstick. Considering the difficult nature of this procedure, it took a long time to perform, and there were concerns that the patient may not tolerate the anesthesia well. We decided to perform the procedure under intravenous anesthesia. Another key factor in this decision was cutting the esophageal wall next to the chopstick[6-8].

The ingestion of foreign bodies is one of the most common endoscopic emergencies in China. However, compared to the cases reported in other studies, this is a special case in that the foreign body was a long chopstick and took us approximately 7 h to complete the procedure. In 2013 (Epub in 2012), we reported the endoscopic management of impacted esophageal foreign bodies and the longest one in this cohort was a 5.5 cm fish bone[1]. In the recent report by Zhang *et al*[9], the mean size of esophageal foreign bodies was less than 2 cm and the endoscopic procedure time was approximately 4 min. To date, the case in the present report is the first clinical report of the longest impacted esophageal foreign body

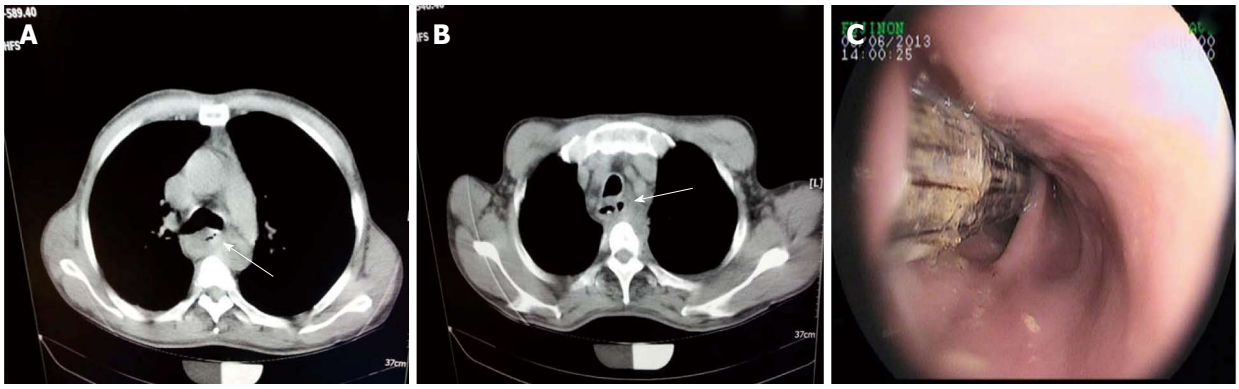

Figure 1 A long chopstick embedded in the esophageal wall. A and B: The roentgenograms showing the foreign body in the esophagus (arrow); C: Endoscopy showing the foreign body in the esophagus.

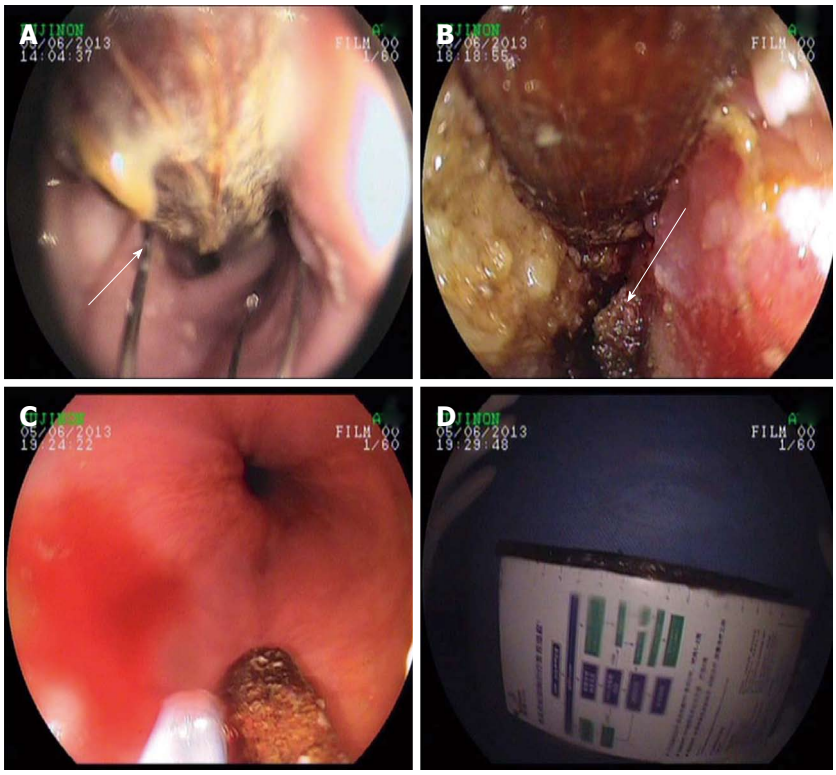

Figure 2 Endoscopic retrieval of the chopstick. A: A snare was tentatively used to remove the chopstick (arrow); B: Hot hemostatic forceps cutting the distal end of the chopstick in the lower esophagus (arrow); C: The freed distal end of the chopstick; D: The 18 cm chopstick measured by a ruler after removal from the esophagus.

removed by endoscopy. Li *et al*[6] stated that when foreign bodies were deeply fixed in the esophageal wall, it was better to avoid any endoscopic attempts and to resort to surgery. However, according to our experience, impacted esophageal foreign bodies can be extracted even when they are fixed in the esophageal wall[1]. Compared to surgery, endoscopic retrieval is minimally invasive and economical, especially in patients older than 60 years, although the procedure time can sometimes be long.

In conclusion, we report our experience of retrieving an 18-cm long chopstick which was lodged 4 cm in the esophageal wall for > 10 mo. To our knowledge, this is the first clinical report of this type of retrieval in a single case.

COMMENTS

Case characteristics

Exacerbated vomiting and fever was described.

Clinical diagnosis

A chest computed tomography (CT) scan revealed the tip of an esophageal foreign body as well as a bilateral lung infection and gastroscopy revealed a chopstick with both ends lodged 4 cm in the esophagus wall.

Differential diagnosis

The gastroscopy confirmed a foreign body in the esophagus.

Laboratory diagnosis

Blood tests were performed routinely and no major clues were found.

Imaging diagnosis

A chest CT scan revealed the tip of an esophageal foreign body.

Treatment

Endoscopic retrieval of the chopstick.

Experiences and lessons

Endoscopy is an effective and minimally invasive treatment for similar cases.

Peer review

This is a very interesting, original case report presenting utility of gastrointestinal endoscopy in diagnosis of psychiatric patient and demonstrating advantage of collaboration between psychiatrists and other clinicians, in management of patients with mental disorders. It is important in face of the fact that this collaboration is very often neglected. This paper is well written and endoscopic procedure is described in detail. The results are clearly presented.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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