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Review

Hydrogen Peroxide Wound Irrigation in Orthopaedic Surgery

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Abstract

As the burden of deep hardware infections continues to rise in orthopaedics, there is increasing interest in strategies for more effective debridement of colonized tissues and biofilm. Hydrogen peroxide has been used medically for almost a century, but its applications in orthopaedic surgery have yet to be fully determined. The basic science and clinical research on the antiseptic efficacy of hydrogen peroxide have demonstrated its efficacy against bacteria, and it has demonstrated potential synergy with other irrigation solutions such as chlorhexidine and povidone-iodine. While hydrogen peroxide is effective in infection reduction, there are concerns with wound healing, cytotoxicity, and embolic phenomena, and we recommend against hydrogen peroxide usage in the treatment of partial knee replacements, hemiarthroplasties, or native joints. Additionally, due to the potential for oxygen gas formation, hydrogen peroxide should not be used in cases of dural compromise, when pressurizing medullary canals, or when irrigating smaller closed spaces to avoid the possibility of air embolism. Finally, we present our protocol for irrigation and debridement and exchange of modular components in total joint arthroplasty, incorporating hydrogen peroxide in combination with povidone-iodine and chlorhexidine.

Key words: Infection, Antiseptics, Hydrogen peroxide, Irrigation, Complications.

Introduction

Deep surgical site infection (SSI) remains a challenging and devastating problem in orthopaedic surgery. The implantation of hardware devices can result in difficult to treat infections, often necessitating reoperations and prolonged antibiotic therapy [1, 2]. An episode of infection places a significant strain on the patient, physician, and healthcare system. In complex spine surgery, the incidence is approaching 10% [3, 4], and in arthroplasty, the infection burden is continuing to rise [5] with increasing bacterial resistance, surgical complexity and patient comorbidities.

Although complete removal of foreign hardware and nonviable tissue is widely considered the gold standard for infection eradication, acute infections may be amenable to aggressive irrigation and debridement, modular component exchange, and hardware retention before bacterial glycocalyx becomes entrenched. Surgical reduction of bacterial bioburden can potentially control the infection by shifting balance in favor of the host immune system and antibiotic therapy, while minimizing morbidity related to hardware removal. The holy grail in the field of infection management is to optimize the feasibility of a single stage procedure, thereby minimizing morbidity to the patient, while maintaining infection cure rates. To this end, various strategies have been implemented to enhance the success of an irrigation and debridement procedure. These are: 1) maintaining separate clean and contaminated instrument sets, 2) enhanced thoroughness and adequacy of debridement, 3)

culture directed antibiotics and local antibiotic delivery, and 4) adjunct antiseptics to cleanse the surgical wound and retained implants.

One method of surgically reducing the bacterial load is irrigation with antiseptic agents [6, 7]. One advantage of antiseptic agents over topical antibiotics is that they are less selective in their action, and are less likely to result in infection with resistant organisms [8]. The associated downside is their cytotoxicity to normal host tissue [9, 10]. In this paper, we will review and discuss the use of hydrogen peroxide as one adjunct for reducing infectious burden in orthopaedic surgery. We will discuss the history of its use, basic science mechanism of action, as well as clinical results.

Historical Use

Hydrogen peroxide was first discovered in 1818 by Louis Jacques Thenard, a French chemist [11]. He named it "eau oxygene" or oxygen water, aptly describing its composition, even though the molecular formula and structure would not be discovered until many years later. It was first produced in pure form in the 1890s and medical use started in the early 1900s. A 1920 Lancet article describes the intravenous infusion of hydrogen peroxide, used to treat broncho-pneumonia on 25 patients in Manchester, England [12]. Their treatment hypothesis was to increase oxygen delivery to cells, while "rendering circulating toxins inert by oxidation". Since that time, hydrogen peroxide has been widely used throughout medicine, surgery and dentistry. Although its ingested and intravenous applications have decreased, it remains a popular topical antiseptic. Compared to other antimicrobial agents, it presents numerous theoretical advantages including its natural occurrence in host tissue, and effervescence which can aid in mechanical wound debridement [13]. It is also cheap and widely available compared to many selective antimicrobial agents, and decomposes into non-toxic by-products.

Basic Science

Mechanism of Action Against Bacteria and Biofilm

Hydrogen peroxide occurs naturally within animal and human tissues and serves various roles in cell signaling, tissue inflammation and aging [14]. Additionally, it is a key component of the innate immune response to infection. Niethammer *et al* [15] in 2009 showed that reactive oxygen species including hydrogen peroxide serve a role in chemical signaling to leukocytes at the site of a wound. Furthermore, hydrogen peroxide combines with chloride to form hypochlorous acid as part of macrophages' and neutrophils' respiratory burst for killing bacteria. [16] It has been shown that enzyme deficient neutrophils incapable of generating these reactive oxygen species are much less efficient at killing many species of microorganisms. A well-known clinical manifestation of this is chronic granulomatous disease, where patients deficient in myeloperoxidase and hydrogen peroxide production are much more susceptible to infection [17].

A 3% solution of hydrogen peroxide demonstrates broad antimicrobial efficacy *in vitro*. Its greatest activity is against Gram-positive organisms, but the catalase enzyme present in these bacteria make dilutions under 3% less effective. [18] *In vivo*, the antimicrobial action can be affected by blood, pus and exudate, which dilute the effective concentration of hydrogen peroxide present. Similarly, catalase is present in normal human tissue and can compromise the efficacy of hydrogen peroxide *in vivo* [19]. Hydrogen peroxide mediated bacterial killing is thought to occur through multiple pathways, including DNA damage [20], as well as oxidation of proteins and membrane lipids [21].

In addition to direct bactericidal activity, multiple *in vitro* studies have shown that hydrogen peroxide can reduce biofilm formation by bacteria [22]. Glynn found that hydrogen peroxide induced stress downregulated biofilm development by *Staphylococcus epidermidis* [23]. Meanwhile, another *in vitro* study found that hydrogen peroxide in combination with sodium hypochlorite actually completely removed or significantly reduced *Pseudomonas aeruginosa* biofilm from stainless steel and aluminum surfaces [24].

Effect on Wound Healing and Host Tissues

One of the main concerns regarding the use of antiseptics is whether they adversely affect host tissues as much as they do foreign bacteria. [25] Tatnall *et al* showed that at antibacterial concentrations, hydrogen peroxide also results in toxicity to keratinocytes and fibroblasts. [26] This has been supported by other *in vitro* studies [27] and one in particular [28] has shown toxicity to chick tibiae and osteoblasts.

Despite these *in vitro* studies, animal and human experiments have shown no *in vivo* deleterious effect on wound healing. In 1975, Gruber *et al* reported accelerated healing of experimental animal wounds as well as skin graft donor sites treated with topical hydrogen peroxide compared to saline or povidone-iodine [29]. Lineweaver found that even though 3% hydrogen peroxide was found to be cytotoxic, it did not adversely affect wound

reepithelialization [30]. Tur *et al* found that topical hydrogen peroxide actually promoted increased vascular perfusion of ischemic ulcers in a guinea pig model [31].

Apart from its effects on wound healing and antiseptic properties, multiple studies have also investigated the effect of hydrogen peroxide on hemostasis in joint replacement surgery with mixed results. Hankin *et al* in 1984 [32] showed that hydrogen peroxide led to less blood loss per unit area when applied to a metaphyseal bone bed in a dog model. A study out of Australia in 1992 showed that hydrogen peroxide irrigation could effectively achieve hemostasis at bone interfaces and improve cement interdigitation [33]. More recently, Chen *et al* investigated the effect of topical hydrogen peroxide and tranexamic acid on blood loss after TKA. They applied 50 mL of 3% hydrogen peroxide after femoral and tibial bone cuts were completed, washed the surface with 0.9% normal saline and dried the bony surfaces in an attempt to reduce bleeding from bone cuts. They found no reduction in blood loss following hydrogen peroxide application compared to controls [34]. Another study on hydrogen peroxide hemostatic effects in an animal model also demonstrated no benefit versus conventional hemostatic techniques [35].

Effect on Implants

One experiment has investigated the effect of hydrogen peroxide on materials commonly used in hip arthroplasty. Shigematsu *et al* [36] soaked samples of ultra-high molecular weight polyethylene (UHMWPE), titanium alloy and hydroxyapatite in 3% hydrogen peroxide and examined the samples under a scanning electron microscope. They found that it had no significant effect on the UHMWPE, and caused a slight darkening of the titanium surface representing an oxidated layer. Meanwhile, they did report etching and concern for erosion of hydroxyapatite. They conclude that the degradative effect on arthroplasty implants is minimal, but caution should be used in cases involving hydroxyapatite coating.

Synergy with other Antiseptics

In addition to its own antimicrobial action, hydrogen peroxide has further been shown to be both synergistic with chlorhexidine and dilute povidone-iodine. Steinberg [37] found chlorhexidine and hydrogen peroxide to be synergistic against species of *Streptococcus* and *Staphylococcus*. They postulate that chlorhexidine may alter the bacterial cell surface allowing increased hydrogen peroxide penetration. Similarly, hydrogen peroxide has been found to act synergistically with povidone-iodine. Zubko observed that at test concentrations, hydrogen peroxide and povidone-iodine proved to be bacteriostatic when used separately, whereas in combination, they were bacteriocidal [38]. They postulate that this is due to metabolic stresses induced by povidone-iodine, which then allows hydrogen peroxide to act unfettered against weakened cells. The significance of antiseptic synergy is that by combining multiple agents, 1) a wider range of organisms can be covered effectively and 2) lower cytotoxic concentrations of the individual compounds can be used.

Clinical Results

Non-Orthopaedic Literature

The effect of hydrogen peroxide on wound healing and infection control has been studied in both general and plastic surgery with mixed results. A randomized trial by Lau *et al* evaluated the effectiveness of hydrogen peroxide on reducing infection rate in appendectomy wounds [39]. It found hydrogen peroxide to be safe to use, but also did not demonstrate any statistically significant change in infection rates. Likewise, another clinical study [40] on human blister wounds contaminated with *Staphylococcus Aureus* found hydrogen peroxide to neither retard wound healing nor effectively decrease bacterial load. Conversely, in plastic surgery multiple studies have shown benefit of hydrogen peroxide on chronic wounds. Mohammadi *et al* in a randomized clinical trial of chronic colonized burn wounds showed that 2% hydrogen peroxide wound cleansing significantly improved skin graft take rates [41]. Another trial by Irkoren demonstrated that hydrosurgery with hydrogen peroxide was superior to controls without hydrogen peroxide for infected wounds, resulting in shorter hospital stay and enhanced graft viability [42].

Orthopaedic Literature

In orthopaedics, the effectiveness of wound irrigation with hydrogen peroxide has been demonstrated in the spine literature. Dauch *et al* filled the surgical wound prior to closure with a solution of 10cc of 10% povidone-iodine + 5cc of water + 1cc of hydrogen peroxide, and then after one minute of action, rinsed it out with copious irrigation with sterile saline to minimize the risk of toxicity [43]. Ulivieri adapted this protocol and performed this systematically over one year. They noted no cases of deep infection out of 490 cases, whereas they had a baseline infection rate of 1.5% (7 of 460) the year prior to institution of this protocol. They noted that hydrogen peroxide was only applied in cases when

the dura was intact to mitigate the risk of air embolism [44].

In the arthroplasty literature, Kosashvili *et al* reported their usage of wound irrigation with a combination of povidone-iodine, hydrogen peroxide and bacitracin [45]. Their overall infection rate was 2.14% in revision cases and 1.35% in first time revisions using this protocol. George *et al* described their protocol for single stage exchange arthroplasty for hip and knee periprosthetic joint infections [46]. They use a combination of 1% povidone iodine and a 50:50 dilution of 3% hydrogen peroxide. Using their protocol, they were able to achieve no recurrences of infection in 11 hips at a mean of 5 years and 28 knees at a mean of 6.5 years.

Hydrogen peroxide has also been applied in orthopaedic oncology and trauma surgery. Wooldrige *et al* used nondiluted hydrogen peroxide as an adjuvant in soft tissue sarcoma resection [47]. They noted statistically insignificant improvement in local recurrence (hazard ratio 0.81, 95% CI 0.27-2.48) and SSIs (0.52, 95% CI 0.15-1.81). Hydrogen peroxide has been shown to be an effective adjuvant on giant cell tumors *in vitro* [48, 49] as well as *in vivo* [50]. There is mixed literature on the efficacy of hydrogen peroxide in preventing external fixator pin tract infection with one trial supporting its use [51] and another showing no difference compared with other cleaning regimens [52].

Special Concerns

The main concerns related to hydrogen peroxide usage pertain to its cytotoxicity and potential for air embolism. Multiple basic science studies have shown that hydrogen peroxide adversely affects articular cartilage by inhibiting normal chondrocyte metabolic function [53-55]. It has been shown to deplete adenosine triphosphate (ATP) in cells, and reduce proteoglycan and hyaluronic acid synthesis in cartilage. While there have been no human clinical studies to our knowledge, these findings are sufficiently consistent that we recommend against hydrogen peroxide usage in the treatment of partial knee replacements, hemiarthroplasties, or native joints. Despite this cytotoxicity towards host tissue, hydrogen peroxide has not been shown to adversely affect the osteoconductivity or structural integrity of allografts when used in the sterilization process [56]. Therefore, it is potentially safe to use hydrogen peroxide with allograft tissue, although we would caution against allograft use if there is any concern for infection.

The other potential serious complication related to hydrogen peroxide relates to its breakdown to form oxygen gas, and the possibility of air embolism. While the effervescence of hydrogen peroxide is considered a unique benefit in terms of providing some aid in mechanical debridement, this can also be a problem in certain circumstances. Since one milliliter of hydrogen peroxide produces about 10 mL of oxygen, this can be deleterious when used in closed cavities [57]. In the spine literature, there have been reports of fatal pneumocephalus [58, 59] when hydrogen peroxide was used for wound irrigation in the lumbar spine. Authors have advocated for hydrogen peroxide use only when the dura is intact, as a dural flap may act as a one-way valve, trapping any oxygen that is produced.

The sequelae of air emboli are also reported in other areas of orthopedic surgery. Timperley and Bracey reported the case of a cardiac arrest following hydrogen peroxide application in an unvented femoral canal prior to cementing [60]. The authors postulate that oxygen bubbles under pressure were rapidly absorbed into the vascular cancellous bone causing air embolism and circulatory collapse. Henley *et al* reported two cases of air embolism leading to circulatory collapse in patients where hydrogen peroxide was used for irrigation of medullary bone after removal of external fixator pins [61].

As a result of these cases, the authors speculate that the irrigation of a closed cavity with hydrogen peroxide is associated with a higher risk than irrigation of an open surgical field. Large volumes of oxygen gas formed in a closed space are pressurized into small vascular channels. An extreme example of this is when hydrogen peroxide is used in neurosurgery after cranial procedures, which represents a closed nonexpendable space in the human body. One report cited a cardiovascular complication rate of 3% in this context [62]. Given these rare but potentially serious risks, hydrogen peroxide should not be used for medullary canal irrigation unless ventilation of the canal is performed. It should not be instilled immediately preceding wound closure, and any application of hydrogen peroxide should be followed by copious wound irrigation to dilute and remove it after a period of activity. A surgical drain is advisable to further decrease the risk of any trapped oxygen gas and lastly, the anesthesiology team should be notified when hydrogen peroxide is utilized intraoperatively to closely monitor for changes in patient oxygen saturation and hemodynamic status.

Practical application

In terms of our own protocol, we currently use hydrogen peroxide as an antiseptic, in cases of irrigation and debridement with modular component exchange (i.e. prosthesis retention) [56]. In these cases,

we find it imperative to reduce bioburden and use hydrogen peroxide as a means to cleanse retained hardware implants. We do not use antiseptics routinely for two-stage procedures or infection prophylaxis in primary or revision cases. In cases where hardware is completely removed and newly replaced, we feel that tissues can be adequately cleansed surgically and mechanically without the added cytotoxicity of antiseptics.

Our antiseptic irrigation protocol consists of five steps. First, the wound is soaked in a 50:50 dilution of 3% hydrogen peroxide and normal saline for three minutes. This is followed by pulsatile lavage irrigation with 3L normal saline. The wound then is soaked in 0.3% dilute povidone-iodine, while continuing to mechanically debride wound with scrub brushes and sponges. After another three-minute period, the wound is again irrigated with 3L normal saline. The final step is soaking the wound with 4% chlorhexidene gluconate. This is followed with repeat irrigation with 3L saline with 500,000 units polymyxin B and 50,000 units bacitracin.

The multistep approach carries several advantages. It is a commonly held surgical tenet that the "solution to pollution is dilution" and by employing multiple steps, we instill a large volume (>9L) of saline through the wound while simultaneously performing mechanical debridement with brushes and a pulse irrigator. Secondly, our multifaceted regimen takes advantage of the synergistic effects of povidone-iodine, chlorhexidine, and hydrogen peroxide. It theoretically decreases risk of bacterial resistance by employing various antiseptic and antimicrobial agents. Lastly, by washing with numerous agents and liters of saline after hydrogen peroxide, we minimize risk of retained hydrogen peroxide at wound closure and consequent risk of air emboli.

Currently, we perform irrigation and debridement along with modular component exchange in a limited subset of patients. These include healthy patients with well-fixed arthroplasty components and a relative acute course of symptoms in the setting of acute postoperative or acute hematogenous infection, or patients who are too medically infirm to undertake a full two-stage exchange. Previous studies have spoken to the importance of microorganism [65-69], timing of infection onset [70-73], and host immune status [67, 74, 75] on the successfulness of irrigation and debridement. At this point, we do not perform any true one-stage exchange arthroplasties, although there is emerging literature support for this practice. [46, 76-79] We believe that hydrogen peroxide and other antiseptic irrigations would be a useful adjunct in this setting based on limited literature.

Conclusion

Irrigation with antimicrobial agents, although widely performed, is selective in its efficacy and can foster development of resistant organisms. Antiseptics, on the other hand, are not as selective but frequently pose cytotoxicity to host tissue that is already compromised in the setting of infection. Hydrogen peroxide carries many theoretic advantages in this regard. It is cheap and widely available, it is naturally occurring in host tissue and decomposes into nontoxic byproducts, its mechanism of action is highly effective and can potentially remove biofilm from implant surfaces, and it has shown to have synergy with other antiseptic compounds. Overall, there is ample general literature to show that hydrogen peroxide does not impair wound healing, and that it may be beneficial for chronically infected wounds. This may suggest that in tissue that is already damaged by infection, the relative antiseptic benefit of hydrogen peroxide outweighs any secondary harm it may produce.

Although hydrogen peroxide has been used medically for over a century, its applications in orthopaedic surgery require further study. While we believe it to be useful in settings of retained hardware, more large-scale clinical studies are needed to determine its effectiveness and safety as an adjunct antiseptic. Much of the existing literature consists of case series, and few reports specifically isolate hydrogen peroxide as the lone study variable. In arthroplasty clinical series for example, it has frequently been used in conjunction with other antiseptics, making it difficult to evaluate the effect of hydrogen peroxide alone. Finally, due to the potential for oxygen gas formation, hydrogen peroxide should not be used in cases of dural compromise, when pressurizing medullary canals, or when irrigating smaller closed spaces to avoid the possibility of air embolism.

Competing Interests

The authors have declared that no competing interest exists.

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