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REVIEW

Acetic acid treatment of pseudomonal wound infections — A review

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Summary
Purpose: Pseudomonas aeruginosa is a significant cause of burn wound infections and, skin and soft tissue infections. The antiseptic management is an integral part of the management of wound infections and is essential to control wound infection. Although commonly used, concerns have been raised.
Results: Available experimental data suggest that many commonly used antiseptic agents may be toxic to the cells involved in wound healing process and may affect the process of normal tissue repair. In view of this, the present review summarized the various organic acids commonly used as a substitute for antiseptics to control pseudomonal wound infections with special reference to acetic acid and their role in the process of wound healing.
Conclusion: Acetic acid is to be kept in mind as one of the alternatives when infection is caused by multiple antibiotic resistant strains of *P. aeruginosa*. At a time when bacterial resistance to antibiotics is a matter of increasing concern, the value of topical agents such as acetic acid should not be forgotten.

Contents

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Introduction

Pseudomonas aeruginosa is a classic opportunistic pathogen with innate resistance to many antibiotics and disinfectants [1]. It is resistant to some common antiseptics and disinfectants such as quaternary ammonium compounds (e.g., cetrimide and benzalkonium chloride), chloroxylenol and hexachlorophane [2,3]. Its isolation has been reported from povidone-iodine, chlorhexidine, dettol and savlon solutions used in hospitals [4—8]. In recent years, *P. aeruginosa* has acquired significance as an important cause of nosocomial infections because of its ability to survive in the hospital environment and because of its ability to develop resistance to antimicrobial agents. It is ubiquitous in the hospital environment and is the most frequently isolated nonfermentative bacillus from various clinical specimens. It can infect almost any external site or organ in the body. It is a significant cause of burn wound infections, and skin and soft tissue infections. Approximately, one third of burn wounds are caused by *P. aeruginosa*. It is an important cause of nosocomial infections and is associated with high morbidity, increased stay in the hospital and increase the cost of treatment because of its resistance to a variety of antipseudomonal agents commonly available. In recent years, an increased frequency of strains resistant to several antimicrobial agents have been reported [9—11]. In spite of continuing introduction of potent antipseudomonal agents, it is the most difficult nosocomial pathogen to be eliminated from infection site. Growing resistance to antimicrobial agents seriously hampers the therapy of pseudomonal infections. The incidence of such multiple drug resistant isolates remains very high in burn units. *P. aeruginosa* is the most commonly encountered and most difficult to eradicate, needs special attention, if uncontrolled, becomes life threatening. There is a substantial evidence that excessive use of antibiotics promotes the selection, propagation and maintenance of antibiotic resistant microbes, especially in the hospital environment. In the recent times, the advent of new antimicrobial agents has helped to decrease the seriousness of many types of infections but in case of nosocomial infections caused by *P. aeruginosa*, the results have been less satisfactory and still the nosocomial infections caused by *P. aeruginosa* present a serious problem. The burn wound infections and, skin and soft infections caused by *P. aeruginosa* are very difficult to treat, in spite of availability of newer antibiotics with broad spectrum of activity. Thus, *P. aeruginosa* continues to create a threat to patient care [1—3,7,8,11].

Local wound care agents (antiseptics)

The optimal topical treatment is a balance between microbicidal activity and tolerability. Generally, highly reactive antiseptics are estimated as too toxic (though there are reports on the usability of agents like hypochlorous acid). Modern antiseptics are less reactive and need a little longer killing times against pathogens but are still efficient.

To the clinician it is obvious that reducing the number of bacteria in wounds is ultimately aimed at accelerating wound healing. The antiseptic management has a dichotomous history anchored in tradition and science. It is an integral part of the management of acute as well as chronic wounds [12,13]. The ideal topical therapy is aimed at reduction of bacterial contamination and removal of soluble debris without adversely affecting cellular activities vital to wound healing process. Although several studies support the value of topical antimicrobial agents, many commonly used antiseptic agents are not approved for use in wound infections. The safety and efficacy of many antiseptics as topical agents for local wound care is a questionable issue. A number of experimental studies both in vitro and in animal wounds suggest that many antiseptic agents including iodine, chlorhexidine, hydrogen peroxide, alcohol, silver sulfadiazine, mefenide acetate, sodium nitrate, sodium hypochlorite, etc. may be toxic to the cells involved in wound healing process. Available experimental data suggest that the antiseptics such as hydrogen peroxide and iodine are not only toxic to fibroblasts but also potentially retard the contribution of fibroblasts

in healing process [14,15]. Repeated and excessive treatment of wounds with antiseptic agents, except for short-time application to attack the causative pathogens and to control the infection, may have negative outcomes or promote a microenvironment similar to those found in chronic wounds [15].

Silver sulfadiazine has a broad spectrum of antibacterial, antifungal and antiviral activity. It is the most commonly used antiseptic agent in burn wound management but it is toxic to fibroblasts in culture [16]. Also, it requires frequent dressing changes, delays re-epithelization and stains tissue. It may also cause allergic reaction and transient leucopenia [17].

Mefenide acetate (sulfamylon) has a broad antibacterial spectrum and has ability to penetrate eschar, its disadvantages include occasional pain on application and inhibition of epithelization [18,19].

Silver nitrate also has a broad antibacterial spectrum but its application to wound can slow down the process of epithelization [20].

Betadine (povidone-iodine) is most commonly used antiseptic agent. It covers a broad antibacterial and antifungal spectrum but in most instances, it does not effectively promote good wound healing. Most studies show that it impairs wound healing and reduces wound strength [20]. Cooper and Laer observed that betadine solution tested at multiple dilutions was found to be most toxic of all agents tested on fibroblasts [21] and has deleterious effect on wound epithelization when used in non-diluted concentrations [22].

Dakin's solution containing hypochlorite (dilute bleach) has a broad antibacterial activity but is toxic to fibroblasts and it has been found that wound treated with Dakin's solution were significantly slower to epithelize and neovascularize [23—25]. It also retards collagen synthesis and delays epithelization, and also inhibits migration of neutrophils in a wound bed, thus undermining the body's natural defense system [22]. They are toxic to tissues because they oxidize tissue enzymes [26].

Antiseptic agents such as hydrogen peroxide, iodine and alcohol and others are also cytotoxic and retard wound healing process [27,28]. Hydrogen peroxide disrupts new capillaries in granulation tissue and also it oxidizes wound debris, and it is toxic to fibroblasts [22].

Dilute acetic acid though successfully used by many workers for the treatment of wound infections caused by *P. aeruginosa*, Lineaweaver et al. showed that a 0.25% acetic acid solution killed 100% of exposed fibroblasts in an in vitro model so that impaired wound healing would be expected at any clinically effective concentration. Acetic acid has also been shown to slow down the wound epithelization and to limit polymorphonuclear — neutrophil function [29].

As reported by various workers, these agents are cytotoxic, retard healing and can do more harm than good when they are not used in a proper concentration. They can interfere with the normal healing process, are toxic to fibroblasts and may permit more virulent microbes to dominate [30]. The result of these observations has been that the use of antiseptics is now often criticized practice; however use of antiseptics at a concentration that is effective and well tolerated, and discontinuation of application as soon as the clinical signs of infection disappear, can be practiced.

Acetic acid treatment

A variety of chemical agents are available, which are nontoxic, inexpensive and highly effective against nosocomial strains of *P. aeruginosa*. It has been reported that in some cases of local applications, chemical agents have advantages over antibiotics, especially in controlling hospital strains of *P. aeruginosa*, which are resistant to multiple antipseudomonal agents commonly used in the treatment of pseudomonal wound infections. These agents can be used locally in the treatment of pseudomonal wound infections and the use of antibiotics can be avoided to some extent. Krasilnikov et al. studied susceptibility of *P. aeruginosa* against antibiotics and antiseptic preparations currently used in medical practice and found that in some cases of local application antiseptic preparations have advantages over antibiotics, especially in controlling hospital strains of microorganisms [31]. The topical use of various organic acids such as boric acid, ascorbic acid, citric acid, salicyclic acid and acetic acid for elimination of *P. aeruginosa* from skin and soft tissue infections and from burn infections has been reported by various workers.

Kujath and Hugelschaffer in 1987 used 3% boric acid to treat local pseudomonas wound infections in 30 patients in which antibiotics had been found to yield little lasting success. They applied boric acid locally and achieved a good success in less than six days on an average without any toxic side effects [32]. Adarchenko et al. studied the effect of various antiseptics on *P. aeruginosa* and found that the activity of boric acid was higher against the clinical isolates of *P. aeruginosa* [33].

Mujumdar in 1993 reported use of ascorbic acid in 35 cases with second degree burn injury involving 20—40% of body surface area infected with *P. aeruginosa*. He used 2% ascorbic acid to wash wound thoroughly and to create acidic medium in tropical climate where warm weather and alkalinity of the

medium renders 0.1% silver sulfadiazine less effective. This treatment modality showed a dramatic reduction (88%) in pseudomonas infection from 94% (pre-treatment) to 6% (post-treatment) [34].

In our earlier studies on pseudomonal wound infections, we have used 2—3% citric acid for the successful treatment of burn wound infections, and skin and soft tissue infections caused by *P. aeruginosa* including multiple drug resistant strains not responding to conventional therapies, which included the oral or injectable antibiotics and local wound care by using hydrogen peroxide and betadine. Application of citric acid quickly eliminated *P. aeruginosa* from infection site. Citric acid was found to be simple, reliable, nontoxic, effective and economical approach in the management of superficial infections caused by multiple antibiotic resistant strains of *P. aeruginosa* [35,36]. The salicyclic acid has also been reported effective against *P. aeruginosa* in a concentration of 0.5—2% and in a concentration of 0.5% has been found to be safe and inexpensive topical agent suitable for thermal burns, which are not heavily contaminated [37].

The use of acetic acid has been reported from time to time as a topical agent for the treatment of pseudomonal infections of burns and, skin and soft tissue infections. Dilute acetic acid is used for the treatment of chronic wounds. It is effective against Gram-negative bacteria, especially against *P. aeruginosa*. Clinical antibacterial efficacy requires a concentration of a 0.5% at least. Acetic acid has been successfully used by many workers for the treatment of wound infections caused by *P. aeruginosa*. Though, the results of in vitro studies indicate that acetic acid is toxic to fibroblasts, these results are not considered as decisive. As acetic acid is well tolerated in vivo and gives better results in the treatment of wound infections caused by *P. aeruginosa*, its use has been reported from time to time as an effective topical agent.

In vitro studies on effect of acetic acid

The in vitro effect of acetic acid was studied by various workers using different concentrations of acetic acid against the clinical isolates of *P. aeruginosa* isolated from patients suffering from pseudomonal wound infections. Husain et al. were first to analyze the sensitivity of *P. aeruginosa*, isolated from burn wound swabs, to various topical agents and found that acetic acid was one of the agents active against *P. aeruginosa* in in vitro studies [38]. Sloss et al. studied in vitro activity of acetic acid in a concentration of 0.1—10%, either applied to the surface of agar plates or placed in wells cut into the agar. Plates were incubated at 37 °C for 18 h and observed for zones of inhibition after incubation. They found that acetic acid at a concentration of 2% was highly effective against *P. aeruginosa* [39].

In our earlier studies on determination of the minimum inhibitory concentration (MIC) of acetic acid, each isolate of *P. aeruginosa* was inoculated into peptone water and incubated for 4 h. After incubation, turbidity of peptone water was matched with McFarland standard No.1 and adjusted accordingly. A set of five test tubes was taken to study the effect of five different concentrations of acetic acid (1—5%). A 100 μL of peptone water culture was taken in five tubes and 100 μL of five different concentrations were added to five different tubes. After proper mixing, subcultures were made on pseudomonas isolation agar (PIA) after 5, 10 and 15 min of exposure. The PIA plates were incubated at 37 °C and after overnight incubation plates were observed for growth. In our studies, a concentration of 3% acetic acid was found to have bacteriostatic activity against *P. aeruginosa* including multiple antibiotic resistant strains [40,41].

In vitro susceptibility to acetic acid was also studied by Juma et al. by using different concentrations of acetic acid (0.5—2%) and reported highest zone of inhibition (18 or more) at a concentration of 2% [37].

Methods of application

Sloss et al. applied sterile gauze swabs soaked in acetic acid (in dilutions of 1—5%) to the ulcers and to smaller burn wounds for 15 min twice daily for 1—2 weeks. In addition bath water containing approximately 0.5% acetic acid was used to immerse each of 4 patients with purulent burn wounds for 22—45 min each day; during this time wounds were debrided [39]. In our studies, based on MIC value of 3% in in vitro studies, 3% acetic acid was prepared by adding 3 ml of acetic acid to 97 ml of sterile distilled water and the following steps were used for its application:

1. Irrigation and washing of wound with normal saline.
2. Placing of a sterile gauze soaked in acetic acid over the wound.
3. Dressing of the wound.

In this way, acetic acid was applied once daily or on alternate days based on the severity of wound infection (daily once in a severely infected wound and on alternate days in a less severe wounds) until the wound healed completely [40,41].

In another study, a dilute vinegar and water solution were found to be superb means of eradicating

local *P. aeruginosa* wound infections. It was used as an irrigating solution or a foot soak in infected necrotic wounds, particularly if associated with *P. aeruginosa* or anaerobic flora. In this study, a commonly used dilution was 15 ml of 5% acetic acid per 200 ml of water or saline for foot soak for 10—15 min [42].

Studies on human pseudomonal wounds

Philips et al. was first to report use of acetic acid as a topical agent for the treatment of superficial wounds infected by *P. aeruginosa* [43]. Sloss et al. reported topical use of acetic acid at concentrations between 0.5% and 5% to eliminate *P. aeruginosa* from the burn wounds and soft tissue wounds. They found that all strains of *P. aeruginosa* exhibited a minimum inhibitory concentration of 2% in vitro. They successfully eliminated *P. aeruginosa* from wounds of 14 of the 16 patients within two weeks of treatment. Acetic acid was shown to be an inexpensive and efficient agent for the elimination of *P. aeruginosa* from burn and soft tissue wounds [39].

In our earlier studies, use of 3—5% acetic acid showed encouraging clinical changes in pseudomonal wound infections. Application of 3—5% of acetic acid to wounds, which were not responding to conventional therapies, which included the oral or injectable antibiotics and local wound care by using hydrogen peroxide and betadine, successfully controlled infections by *P. aeruginosa* thereby eliminating them from local site of wound and caused successful healing in 5—12 applications without any adverse effects [40,41].

Al-Ibran and Khan in 2010 studied the effect of 1% acetic acid in burn wounds in eradication of *P. aeruginosa* infection and found that application of acetic acid for 10—14 days cleared *P. aeruginosa in* 90% of cases [44].

Conclusion

Acetic acid was found to have bacteriostatic activity against *P. aeruginosa*, including multiple antibiotic resistant strains of *P. aeruginosa*. Acetic acid in a concentration of 0.5—5% was found efficient in elimination of *P. aeruginosa* from superficial infection site. Such local antiseptic preparations have advantages over antibiotics in that their use does not encourage evolution of multiple drug resistant strains of microorganisms in hospital environment.

It is to be kept in mind as one of the alternatives when infection is caused by multiple antibiotic resistant strains of *P. aeruginosa*, in which there is shortage of therapeutic options. At a time when bacterial resistance to antibiotics is a matter of increasing concern, the value of topical agents such as acetic acid should not be forgotten.

Further clinical trials using suitable control groups treated with antiseptics or antibiotics for comparison will help in achieving more useful and concrete conclusions regarding the efficacy of acetic acid in controlling wound infections caused by *P. aeruginosa* including multiple antibiotic resistant strains. Hence, such clinical trials involving suitable control groups are recommended.

Conflict of interest

None to declare.

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