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Topical Antimicrobials and the Open Surgical Wound

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Abstract

Background: Topical antiseptic and antibiotic agents have been used for the prevention of surgical site infections since Joseph Lister's original research on this subject. Although these agents are used extensively in clinical practice, evidence to support the use of topical antimicrobial agents remains limited.

Patients and Methods: The world literature on the use of antiseptic and antibiotic agents was evaluated to determine the current status of evidence to support the use of topical antimicrobial agents in the prevention of surgical site infections.

Results: Although several techniques of using topical antibiotic solutions, powders, antibiotic gauzes, and beads have some evidence for validation, there are equal numbers of reports that have failed to show benefit. There is little evidence to support the use of antiseptic solutions in the prevention of infections at the surgical site.

Conclusions: Additional clinical trials are necessary to provide evidence to support any of the methods for using topical antimicrobial agents to present surgical site infections. Dilute antiseptic agents should be considered in future trials when antimicrobial activity can be identified without local toxicity.

SURGICAL SITE INFECTION (SSI) continues to be the source of complications after all operative procedures. Numerous preventive strategies are used to prevent SSI, because there are a variety of potential sources of bacterial contamination and there are an abundance of clinical risk factors that will enhance the virulence of micro-organisms that are present at the surgical site [1]. The prevalence of bacteria from patients, the operating team, and the environment means that all surgical sites have organisms that can be cultured at the end of the procedure.

It has always seemed logical that the introduction of antimicrobial agents into the wound at the completion of the operation ought to be of benefit in the reduction of infection post-operatively. The French barber surgeon, Ambroise Paré (1510–1590) [2], used topical egg yolk, oil of roses, and turpentine as an alternative to boiling oil for the management of open traumatic wounds. Numerous alternative agents have been used both to create and prevent "laudable pus" in surgical and traumatic wounds well before the germ theory of disease evolved.

With the evidence by Pasteur and others of the role of microbes in infection [3], it was Joseph Lister who introduced topical antiseptics (carbolic acid) as a method to reduce infections in the open surgical incision. As was identified by Lister [4] in one of his last publications, however, the benefits of antiseptics in the open wound were offset in part by the

"caustic action which I knew must occur." Nevertheless, the early benefits for the reduction of SSI rates with the use of carbolic acid in preparation of the skin and sterilization of instruments led to the expectation that clinical benefit could be derived from the introduction of topical antimicrobial agents into the open incision and that these benefits might override potential local tissue toxicity.

Potential Topical Antiseptics

The potential topical antiseptic agents that have been proposed for use in the open surgical incision or traumatic wound for the prevention of infection are identified in Table 1. The advantage of the topical application of an antiseptic agent is the achievement of high concentrations of the agent at the site of bacterial contamination. As a group, the antiseptic agents have rapid and bactericidal effects on most potential bacterial pathogens that will contaminate the open incision. Antiseptic agents have multiple mechanisms of action on the bacterial cell, which gives them a broad spectrum of antimicrobial activity and also makes the emergence of resistant strains uncommon.

As a group, the antiseptic agents are chemicals, not of biologic origin, and tend to be hypoallergenic. In addition to the use of antiseptic agents for the prevention of infections in open incisions, many of the agents in Table 1 have been used

Table 1. Antiseptic Agents Applied to Open Surgical Incisions that Have Been Used to Prevent or Manage Post-Operative Surgical Site Infection

Antiseptic choice	Comments
Acetic acid solution	Dilute (0.25%) solutions have been used in incisions without any evidence to support use. Higher concentrations are associated with tissue injury. The solution has been used in bladder irrigation and for otitis externa management.
Alcohols	Isopropyl alcohol is most commonly used for topical skin application. Rapidly bactericidal. Desiccates open incisions and is tissue toxic; painful in most concentrations. Not recommended for use in open incisions.
Boric acid	Used as eye irrigation for its antimicrobial effects, it is not recommended for use in open incisions.
Chlorhexidine	The most common antiseptic in skin preparations, it is generally not recommended at conventional concentrations of 2%–4% in open incisions.
Chlorine compounds	Buffered sodium hypochlorite solution; used at 0.25%-0.5% solution; action from oxidative injury of bacterial membranes and enzymes.
Hydrogen peroxide	A common household remedy for cuts and abrasions, it is generally tissue-toxic for application in open incisions for prevention.
Iodine compounds	Tincture of iodine has largely disappeared for any application in operations. Iodophors are less toxic. Iodophors have been used clinically for topical application in open incisions but have not been subject to clinical evaluation for efficacy.
Silver compounds	Silver nitrate and silver sulfadiazine have been extensively used in burns and selectively in open infected soft tissue incisions. Various slow-release topical preparations are available but are not used commonly in open incisions for prevention.
Triclocarban	A common antiseptic in commercial soaps; there are no data to evaluate its use in open incisions.
Triclosan	Common antiseptic in cosmetics and used in the coating for selected surgical sutures. No data on use in open incisions.

extensively in chronic or actively infected soft tissue wounds (e.g., Dakin solution). The randomized clinical evidence to document clinical effectiveness is lacking, however, and continued practice in using these topical agents in the chronic wound is largely based on testimonials and anecdotes.

The antiseptic agents collectively are viewed with negative features that have been deterrents for their use in the acute surgical incision for prevention. As was noted by Joseph Lister, the antiseptics have a concentration-dependent tissue toxicity. Antiseptic agents commonly contain detergents that may contribute to local toxicity in the tissue. There is a considerable volume of literature that speaks to the issue of tissue cytotoxicity [5,6] and inhibition of wound healing [7].

Finally, there are limited data that would support the use of topical antiseptic agents in the incision for the prevention of SSI. Randomized trials are rare and usually underpowered. In the era of systemic antibiotic agents, there has been very limited interest in pursuing clinical trials to evaluate specific antiseptic agents that are introduced into the incision for the prevention of infection in surgical incisions or traumatic wounds. The role of antiseptic agents has largely been relegated to the preparation of the skin before the surgical incision or placement of a percutaneous device.

Topical Antibiotics

With the discovery of sulfa and penicillin, many clinicians viewed the topical application of these agents as potentially of benefit in the prevention of SSI. Topical antibiotics permit concentrations of the drug in the incision that would be much greater than systemic administration. The topical use avoids or markedly limits any systemic exposure of the drug and has the promise of not creating resistance problems that are associated with parenteral use.

The problems of topical antibiotic application in the open incision are several. First, there is no convincing evidence that topical antibiotics improve on the benefits that are observed with the appropriate use of systemic preventive antibiotic agents. Second, because high concentrations are used with topical application, there are the usual concerns about potential toxicity and inhibition of wound healing. Finally, the application of topical antibiotic agents has usually been performed by adding the drug to a volume of saline irrigation and then applying the antibiotic solution to the incision.

Customarily, this is performed with the dwell time of the antibiotic-laden irrigation only a brief period (15–30 sec) at which point the solution is suctioned from the area. Unlike antiseptics, the contact of the antibiotic with the bacterial target necessitates a time for biologic effect that is far greater than the dwell time that is commonly used. Thus, it is unlikely that the antibiotic irrigation solution has much of an effect on the microbial inoculum in large part because of the methods of delivery that have been used in clinical practice.

A scenario that attempted to address this shortcoming of topical antibiotic solutions was that of Lord et al. [8] in which the antibiotic was applied every 10 minutes during the operative procedure. This later scenario was viewed as logistically not practical during a long operation and was not evaluated against appropriate systemic antibiotics in a controlled clinical trial.

Alternative Topical Delivery Systems

The problems of topical delivery of antibiotics to achieve a sustained concentration of the drug to optimize the opportunity for prevention at the surgical site have led to several alternative methods other than simple incision irrigation. An innovative method for delivery of an antibiotic solution for

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prevention of SSI has been proposed by Alexander et al. [9] in patients undergoing open gastric bypass operations. Closed suction catheters are introduced by separate stab incisions and are placed in a dependent position within the surgical incision space after fascial closure. The skin of the incision is then closed in a watertight fashion.

Kanamycin irrigation solution (0.1%, or 1,000 mcg/mL) is then introduced through the suction catheters to create a liquid environment of concentrated antibiotic within the space. The irrigation solution remains for 2 hours and then is suctioned out. This technique has the promise of overcoming the transient antibiotic exposure of the contaminating bacteria that occurs with conventional irrigation and suctioning at the end of the operation but before wound closure.

Results of the alternative irrigation tactic in more than 800 patients with an average body mass index >50 have demonstrated reduced SSI rates (<0.25%) in this high-risk population of patients undergoing a bariatric procedure compared with historical control groups. This methodology may well have merit in those patients undergoing laparotomy with substantial depth of subcutaneous adipose tissue but would likely be of limited value in thin patients. Additional studies are necessary to evaluate this method, the length of time that would be best for achievement of optimal outcomes, and which antibiotic would be best suited for topical delivery.

Instead of using an antibiotic irrigation solution, some have used undissolved antibiotic powder and directly introduced it into the incision at the time of closure. Andersen et al. [10] introduced ampicillin powder into the incision after surgical removal of non-perforated appendices and reported a dramatic reduction in SSI rates compared with patients treated with incision closure alone. Andersen et al. [11] similarly reported a dramatic reduction in SSI rates after colorectal surgery with the use of ampicillin powder in the incision at closure.

Raahave et al. [12], however, reported no benefit in the prevention of SSI in patients undergoing colon resection using the same application of topical ampicillin powder. The use of antibiotic powder continues to be discussed, but convincing evidence for using such a tactic in high-risk surgical incisions (e.g., colon resections) is not available.

Antibiotic-impregnated sponges and fleeces that are made of biodegradable collagen have been introduced into the surgical incision at closure in the hope of achieving a sustained release of drug into the incision interface. In a randomized trial of 221 patients who were undergoing elective colorectal surgery, the use of the gentamicin-impregnated sponge reduced SSI rates to 5.6% compared with patients without the sponge (18.4%; p<0.01) [13]. Greussner et al. [14] found a reduction in perineal SSIs in patients undergoing abdominoperineal resection when an antibiotic-impregnated fleece was place in the incision at primary closure.

In another randomized clinical trial by Bennett-Guerrero et al. [15] of 602 patients undergoing colorectal procedures, the gentamicin sponge was identified with an increased SSI rate of 30% compared with no sponge placement of 20.9% (p=0.01). In a study of nearly 2,000 patients undergoing cardiac operations, the use of the gentamicin sponge was reported by Friberg et al. [16] to dramatically reduce surgical SSIs. Schimmer et al. [17], who studied more than 700 patients who were randomized to receive a gentamicin sponge behind the sternum at closure compared with no sponge,

noted a reduction of deep sternal incision infections from 3.5% to 0.6%.

A study by Bennett-Guerrero et al. [18] of 1,500 patients undergoing cardiac surgery identified no reduction in SSI rates with the use of the gentamicin-impregnated sponge. Eklund et al. [19] found no reduction of SSI in a study of 542 cardiac surgery patients who were randomized to the gentamicin sponge versus standard closure.

Thus, there are conflicting data on the utility of the gentamicin-impregnated collagen sponges/fleeces into the surgical incision to prevent SSIs. There is certainly variability in the methods used for placing the collagen matrix in the incision, and this may account for some differences in results. The foreign body effect could create an adjuvant effect to enhance infection rates. The inflammatory response surrounding the biodegradation of the collagen material combined with a variable inoculum of bacteria can lead to exudative discharge from the closed incision that may or may not be clinical infection. The collagen material may potentially create a sustained dead space in the wound after closure. Creanor et al. [20] found insufficient evidence to support the use of gentamicin sponges for cardiac operations in a metaanalysis of clinical trials. Overall, the current evidence does not support using this method.

Antibiotic-impregnated cement has been evaluated in multiple studies of total joint replacement. Parvizi et al. [21] evaluated seven studies by meta-analysis in which antibiotic-impregnated cement was used and identified a significant reduction (p<0.001) in SSI. Gentamicin was the predominant antibiotic agent used. Others have reported no benefit with this method in a study of 3,000 patients in which erythromycin and colistin-impregnated cement was used [22]. Antibiotic-impregnated cement is used in practice, but additional studies are necessary to evaluate the correct formulation of the antibiotic agent employed and the concentration to optimize outcomes.

Antibiotic-impregnated beads are used by selected orthopedic surgeons for the prevention of SSI in open fractures. The beads are made with methylmethacrylate and have impregnated aminoglycoside or other antibiotic agents. Combination drugs are often used. The beads are placed into the incision and the antibiotic agent diffuses out of the beads and into the adjacent tissue giving a sustained release over time. The beads are then removed once healing is complete. The beads are used for open fractures, management of osteomyelitis, and for management of dead space in orthopedic procedures.

Ostermann et al. [23] reported a reduction in SSI from 12% to 3.7% with the antibiotic beads in open fractures. Moehring et al. [24], however, found no benefit from using antibiotic beads in the prevention of infection in open fractures. Bioabsorbable beads are now being evaluated [25]. In a review of using antibiotic-impregnated beads in open fractures, Hauser et al [26] concluded that there was "insufficient evidence to support the routine use of antibiotic-impregnated beads as prophylaxis in open fracture surgery."

There are many published and unpublished methods that have been used for the delivery of antibiotic agents into the open surgical incision to prevent infection. The collective data remain inconclusive to use any method. The problem remains that many different antibiotic agents are used, and all have their peculiar method for drug delivery. Studies that

report benefit have high infection rates in the control groups, and many of those reporting no differences in infection rates often are underpowered. Several of these methods may ultimately prove to be of benefit. Huiras et al. [27] and McHugh et al. [28] have concluded that evidence is insufficient to support any topical used of antibiotics to prevent infection. Systemic antibiotics remain the preferred choice for prophylaxis of SSI.

Antiseptics Revisited

The search for an effective topical antimicrobial tactic has struggled with insufficient evidence to justify any use [29]. The problem of topical antiseptics has been the local tissue and phagocytic cell toxicity of the agents that have been used. An area that has been ignored largely is whether an antiseptic concentration can be identified that has potent antimicrobial activity but does not have clinically significant local tissue or host response injury.

Chlorhexidine solution is the topical antiseptic that is generally used for skin preparation of surgical sites and for insertion of intravascular devices. The conventional preparations are 2% or 4% solutions. Dental mouthwashes have only a 0.12% concentration and appear to have antimicrobial effect but without adverse effects on mucous membranes.

Edmiston et al. [30] evaluated the in vitro antibacterial effects of 0.05% chlorhexidine solution on multiple bacterial strains. The authors identified a five-log₁₀ reduction in bacterial colony-forming units when a 10⁸–10⁹/mL concentration of *Staphylococcus* and *Escherichia coli* was exposed to 0.05% chlorhexidine. These observations pose an interesting question for the topical use of this antiseptic at a concentration that is not recognized as having local tissue toxicity.

Yet another feature of chlorhexidine is the binding of the antiseptic agent to soft tissue. Chlorhexidine binds to epidermal, mucous, and subcutaneous tissues after topical application. The bound chlorhexidine has antiseptic effects that continue after the tissue binding, and it is unaffected by the local presence of blood [31]. As a dilute irrigation solution of open wounds and soft tissue infections, it can be anticipated that antiseptic effects will continue after application.

To explore these potential advantages in the prevention of SSI, a clinical trial is being conducted to test whether 0.05% chlorhexidine applied by a unique application to the open surgical incision will reduce SSI rates. The study is being performed with the IrriSept® system for topical administration [32]. This system contains 450 mL of 0.05% chlorhexidine in water. The delivery system consists of a hand-held compressible bottle that allows delivery of the antiseptic irrigant under pressure to provide both the antiseptic but a pressure-lavage effect on the wound surface.

The pressure-lavage effect offers a debriding effect on the wound surface, but at a lower pressure than is observed with conventional pulsed-lavage systems. This lower pressure lavage affords removal of the contaminated fibrin surface of the wound but avoids the pressure-associated tissue injury that has been observed with high-pressure irrigation systems. The low pressure administration permits tissue penetration of the dilute antiseptic that may have merit for both the prevention and management of soft tissue infection.

In the current trial, patients presenting with emergency trauma and those undergoing emergency open laparotomy will be enrolled and randomized. These operations are chosen because SSI rates can be anticipated to be ≥20% when the surgical incision is closed primarily. This trial of open contaminated emergency laparotomy incisions will test the hypothesis of reducing SSI rates with the IrriSept irrigation system versus conventional irrigation and incision management. Patients in both arms of the trial will receive appropriate pre-operative systemic antibiotic agents, and systemic antibiotic therapy will be discontinued within 24 hours of the procedure. The study will have a total of 600 patients randomized to either the IrriSept or conventional (pour/bulb syringe) application.

Each patient in the trial will have irrigation of the incision at two standardized times. The initial irrigation will be after the incision is made but before the abdominal fascia is opened. A 60-second dwell time will be required after this initial irrigation. This initial irrigation will test the hypothesis of whether tissue penetration and tissue binding of the Irri-Sept system is superior to conventional irrigation. At the conclusion of the operative procedure, the fascia will be closed by the standard method of the operating surgeon and either the IrriSept or standard irrigation will be conducted a second time. A dwell time of 60 seconds will again be used after the second irrigation.

Comprehensive clinical data including pre-operative laboratory data will be obtained to permit risk adjustment of the patient population. There will be 12–15 study centers. SSI of the incision is the primary evaluation end point at 30 days after the operation. An initial analysis by an independent contractor will be performed after a total of 350 cases have been randomized and evaluated.

Conclusion

Although the benefits of preventive systemic antibiotics are well accepted, it is generally perceived that better outcomes can possibly be achieved by the addition of topical antimicrobial agents at the surgical site. Studies to validate the added benefit of topical agents have been inconsistent and generally viewed as not being conclusive in their results. The failure of topical antimicrobial agents to augment systemic antibiotic agents may well be shortcomings of the delivery system. Better clinical trials that are adequately powered, that examine different delivery systems, and examine drug dosage and exposure are necessary to find a topical antimicrobial tactic that will improve outcomes.

Author Disclosure Statement

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