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Review

Local Intra-wound Administration of Powdered Antibiotics in Orthopaedic Surgery

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Abstract

Surgical site infection (SSI) is one of the most common complications after orthopaedic surgery, leading to significant morbidity and its associated costs. Surgical guidelines strongly recommend the use of systemic antibiotic prophylaxis to reduce the risk for developing SSI. Locally administered powdered antibiotics have the potential to provide remarkably high intra-wound concentrations without risk for systemic toxicity. However, a paucity of high quality evidence in the orthopaedic literature has prevented widespread adoption of this technique. The majority of clinical studies on local intra-wound antibiotics have evaluated the use of topical powdered vancomycin in spinal surgery, though only a single prospective study currently exists. This review will discuss all the available evidence describing the effectiveness, pharmacokinetics, and potential adverse effects with the use of topical powdered antibiotics in orthopedic surgery.

Key words: Surgical site infection, orthopaedic surgery

Introduction

Infection is one of the most dreaded complications in orthopaedic surgery. Despite careful antiseptic technique, surgical site infection (SSI) has now become the most common and costly cause of healthcare-associated infection in the US, accounting for considerable morbidity and mortality. (1-4) The United States Centers for Disease Control (CDC) National Healthcare Safety Network (NHSN) reported an overall SSI rate of 2% in the US from 2006-2008. (5) According to this same report, SSI occurred in 1.1% of orthopaedic procedures, including 1.05% of elective total joint arthroplasty (TJA), 1.3% of spinal surgeries, and 1.7% of open fracture reductions. (6) Orthopaedic SSIs significantly prolong hospitalizations, increase hospital readmissions and costs, and limit functional and quality of life outcomes. (7) Therefore, both published guidelines and established evidence support prophylactic use of preoperative systemic antibiotics to prevent SSI. (8-13) According to a recent survey of orthopaedic surgeons in Canada, 96.6% indicated routine use of systemic prophylactic antibiotics in TJA, primarily with cefazolin. (14) Not included in most guidelines is the use of local antibiotics for perioperative infection prophylaxis.

Local administration of topical powdered antibiotics was first popularized in the late 1960s for prevention of wound infection in abdominal surgery prior to the existence of effective systemic prophylaxis. (15) Topical antibiotics have also been applied locally in irrigation solutions, ointments, pastes, beads, sponges, and fleeces. (16) Local administration of powdered antibiotics is an attractive method, as it has the potential to deliver exceptionally high doses of antibiotic to the surgical site with less systemic exposure and thus potentially fewer adverse systemic effects. However, there is a dearth of high quality clinical evidence supporting this practice in both the orthopaedic and overall surgical literature. Further, the available literature spans decades during which major changes have been made in surgical protocols. Furthermore, antibiotics and the organisms

they are used to treat have evolved over time. The risk-benefit ratio of local antibiotic application is under investigation. The following is a review of the literature regarding the role of perioperative topical powdered antibiotics used in orthopaedic surgery.

Background

Acute SSI is thought mainly to arise from wound contamination occurring from a small inoculum during the operation. (17) In addition to skin preparation and other sterile techniques, antibiotic prophylaxis reduces the bacterial load at the operative site. This is especially important in the presence of a foreign body. While 10^3-10^5 bacteria may typically be necessary to initiate a bone infection, as few as 10 organisms may be sufficient in the presence of an implant. (18)

Delivery of local antibiotics

Lyophilized powder is just one of several modalities that exist for local delivery of antibiotics. Other common methods used in orthopaedic surgery include irrigation solutions, bone graft and its substitutes, bone cement and cement beads, and natural or synthetic polymers. Additionally, ointments, pastes, and collagen sponges or fleeces have been used in other surgical fields for antibiotic delivery. (15) These modalities vary in their utility and pharmacokinetics, and the most appropriate formulation should be individualized to suit a specific application. Powders have been studied most extensively for applications requiring short-term exposure, such as surgical prophylaxis. Prolonged antibiotic exposure increases risk for systemic toxicity or the emergence of resistance. (19, 20)

Timing of local antibiotics

Local antibiotics are typically not applied until just before closure, which some suggest may limit their use other than as an adjunct to parenteral prophylaxis. There is evidence to suggest that there is a finite period during which prophylactic antibiotics may suppress an incisional infection. A study on experimental incisions in 1961 demonstrated that the effective period lasts for 3 hours from the moment bacteria gain access to tissue and maximal suppression is achieved when antibiotics are given before bacteria gain access to tissue. (21) It is unclear what role adjunctive local antibiotics play in prophylaxis for infection and what the appropriate timing of such antibiotics should be.

Pharmacokinetics

The goal in using local powdered antibiotics is to achieve substantially higher and longer-lasting antibiotic concentrations at the surgical site without exposing the systemic circulation to toxic drug levels. The pharmacokinetic profiles of locally applied powered antibiotics have been documented based solely upon small studies evaluating both serum drug levels and surgical site levels excreted into surgical drains. Three studies observed the pharmacokinetics of vancomycin powder administered locally into surgical spine wounds. (22-24) After administration of 2 grams of vancomycin, surgical site levels during the first day postoperatively reached nearly 1500 mg/L and remained elevated above 100 mg/L through the third day. (22) In contrast, serum levels were undetectable (<0.6 mg/L) in 80% of patients. Similar results were observed with administration of 1 gram of vancomycin topically in pediatric spine patients, with surgical drain levels reaching above 400 mg/L and serum concentrations peaking at a mean of only 2.5 mg/L postoperatively. (24) When administered onto the cut edge of sternotomy wounds, 0.5-1 gram vancomycin slurries reached peak levels in serum of less than 3 mg/L over the first few hours. (25, 26) Serum levels appear to remain considerably below the recommended vancomycin trough concentration of 5-10 mg/L. (25) In addition to vancomycin, the pharmacokinetics of cefazolin were also evaluated in 24 patients undergoing bilateral breast reduction. (27) Patients receiving cefazolin administered locally by wound irrigation achieved a peak concentration at the surgical site that was 186 times greater (nearly 4200 mg/L) than in patients for which cefazolin was administered intravenously. (27) The cefazolin concentration remained well above a typical minimum inhibitory concentration (MIC) well beyond 24 hours, as compared to only 5 hours with intravenous administration. There are no studies specifically on the pharmacokinetics of cefazolin powder. Finally, gentamicin collagen sponges achieved exceedingly high concentrations of greater than 100 mg/L after 8 hours, with serum concentrations below 3 mg/L at that same time point and undetectable in nearly all patients within 48 hours. (28)

Contribution to resistance

It is generally accepted that exposure to antibiotics increases the likelihood of the emergence of drug resistance. (29) Minimizing antibiotic exposure for surgical patients (so-called antibiotic stewardship) is considered to be a best practice. (30) In the setting of topical powdered antibiotics, an increased risk for resistance is theoretical and difficult to quantify. Of particular concern is persistent systemic exposure to sub-inhibitory levels of vancomycin, which may select for resistant strains.

The development of vancomycin-intermediate resistant *Staphylococcus* was demonstrated in an *in vitro* model with persistent vancomycin exposure above 10 mg/L. (31) However, experimental exposures were 5-fold higher than peak systemic levels typically achieved with topical intra-wound vancomycin. Another study evaluated for changes in the microbiologic properties of a methicillin-resistent *Staphylcoccus aureus* (MRSA) strain in a patient receiving chronic exposure to vancomycin for a 9-month period. (32) No resistance was detected, and only minimal changes in vancomycin susceptibility were observed. Finally, the emergence of vancomycin resistance has not been reported in studies on the use of topical vancomycin in spine surgery. (33) As its contribution to resistance is a major public health concern, surgeons must weigh the risks and benefits of using topical antibiotics.

Adverse effects

One of the major attractions of local antibiotics is the prospect of low systemic toxicity. A recent systematic review reported all adverse events with the use of powdered intra-wound vancomycin in spine surgery. (33) Of 6701 patients identified in 16 studies, only 23 complications were reported. Culture-negative seromas were reported in 19 patients, two patients experienced ototoxicity resulting in transient hearing loss, 1 patient had nephropathy, and super-therapeutic exposure was reported for 1 patient. There is also a case report describing circulatory collapse following an anaphylactic reaction to intra-wound vancomycin during a spinal procedure. (34) Another study found topical vancomycin to be safe for use in pediatric spine patients, with no reported anaphylaxis, nephrotoxicity, red man syndrome, thrombophlebitis, or rash. (23)

The effect of antibiotics on bone healing has also been investigated. In an experimental model, the use of local vancomycin, cefazolin, and gentamicin had no significant effect on fracture healing at typical levels achieved with systemic therapy. (16, 35) However, as noted previously, much higher concentrations (>2000 mg/L) may be attained when using local antibiotics. Studies on osteoblast-like cells have demonstrated that concentrations of vancomycin below 1000 mg/L had little or no detrimental effect, but concentrations of 10,000 mg/L caused osteoblast cell death. (36) Cefazolin concentrations of 100 mg/L had no effect, but cell replication was significantly reduced at concentrations of 200 mg/L and cell death ensued at levels above 10,000 mg/L. (36) A similar study on tobramycin demonstrated no effect at concentrations less than 200 mg/L, decreased cell replication above 400 mg/L, and cell death at concentrations greater than 10,000 mg/L. (37) In one meta-analysis, the relative risk for pseudarthrosis with the use of topical vancomycin in spine surgery was 0.87 (p=0.77). (38)

While there is little clinical evidence on the use of topical antibiotics in total joint arthroplasty (TJA), there are some concerns with regard to third-body wear with the addition of a crystalline powder near the implant interface. However, little difference in wear behavior was appreciated when cobalt-chromium and ultra-high molecular weight polyethylene were exposed to 10 million cycles in a wear simulator. (39)

Finally, concern over an increase in wound dehiscence or herniation was evaluated in prior studies on gastrointestinal and vascular surgery. Three studies demonstrated no increased risk with the use of topical ampicillin or vancomycin, though one study reported a trend towards increased dehiscence (6.7% vs. 4.1%) and herniation (10.8% vs. 3.3%). (40, 41, 42)

Clinical evidence in orthopaedic surgery

We have summarized the available clinical studies evaluating the efficacy of topical powdered antibiotics for surgical prophylaxis in orthopaedic surgery. As aforementioned in the Introduction, there is a dearth of high quality prospective evidence evaluating the use of topical powdered antibiotics in orthopaedic surgery.

Spine surgery

The administration of local intra-wound vancomycin has become a routine practice for many spine surgeons. This trend has occurred despite a lack of high level evidence. Of 21 controlled studies published on powdered vancomycin in the literature, only a single study was performed prospectively as a randomized controlled trial. Further, 11 of 20 retrospective studies utilized a pre- and post-intervention design without adequately controlling for potential confounders in the historical control group. Similar to an editorial in 2014, we found that control groups in 8 retrospective studies had SSI rates above 11%, which is several-fold higher than the median rate (3%) in a report on high-risk patients undergoing spinal fusion. (6, 43) Finally, most studies did not use a standardized definition for SSI, and meta-analyses have clearly identified a publication bias indicating that only positive studies have been reported. The currently available evidence is reviewed below.

Meta-analyses

Eight meta-analyses have been published since

2014 reporting on the pooled risk for SSI from up to 16 studies with and without the use of topical vancomycin in spinal surgery. (33, 38, 44-49) Each meta-analysis found a statistically significant improvement in favor of the use of topical vancomycin, with odds ratios for SSI ranging from 0.11 to 0.43.

Randomized controlled trials

One randomized trial was performed from 2011-2012, which included 907 patients who underwent both instrumented and non-instrumented spinal surgery in India. (50) All patients received systemic prophylaxis with intravenous cefuroxime for at least 24 hours postoperatively or until drain removal for instrumented procedures. The intervention group also received 1 gram of topical vancomycin introduced into the muscle, fascia, and subcutaneous tissue. There was no significant difference in the rate of SSI between the control (1.68%) and treatment (1.61%) groups.

Consecutive retrospective cohort studies

Nine retrospective studies reported on a cohort of patients who underwent consecutive spinal procedures with or without topical vancomycin. These studies were quite small, ranging in size from 110 to 389 patients. Six studies demonstrated a statistically significant reduction in the rate of SSI with the use of topical vancomycin, and two additional studies reported a strong trend in favor of topical antibiotics. (51-58) However, one study using propensity score matching demonstrated no difference with the use of topical vancomycin; this was one of only two studies that accounted for potentially confounding variables. (59) Odds ratios for SSI with topical vancomycin ranged from 0.06 to 0.75.

Pre- and post-intervention retrospective cohort studies

Eleven studies employed a historical control group of patients who underwent spinal surgery prior to commencing use of topical vancomycin. While five studies were small, including 300 or fewer patients, there were also several large studies ranging in size from 683 to 3598 patients. Four of five small studies demonstrated a statistically significant reduction in SSI with topical vancomycin, with odds ratios for SSI ranging from 0.02-0.96. (60-64) Similarly, five of six larger studies reported a significant reduction in the rate of infection with topical vancomycin, with odds ratios ranging from 0.08-0.48. (22, 65-69) Only a single study of this type accounted for confounding variables.

While enthusiasm for topical vancomycin may be warranted based upon an accumulation of retrospective evidence, the single randomized controlled trial performed to date reported no difference in the rate of SSI. (50) Well designed prospective studies are needed to provide more rigorous evidence either supporting or refuting the role of local antibiotic application in prophylaxis for SSI.

Total Joint Arthroplasty

A single retrospective clinical study has reported initial results with the use of topical vancomycin for surgical prophylaxis in total hip arthroplasty. (70) 125 consecutive patients who underwent THA received either intravenous cefazolin alone or in addition to 2 grams of vancomycin powder. There was a significantly lower infection rate for patients receiving topical vancomycin, and there were no adverse events reported.

Trauma

A single retrospective pilot study was published using topical intra-wound vancomycin powder for prophylaxis in orthopaedic trauma surgery. (71) Ten out of 93 patients who underwent open reduction and internal fixation for a high-energy tibial plateau or pilon fractures received 1 gram of topical vancomycin in addition to intravenous cefazolin. As compared to 16.8% of patients in the control group, 1 (10%) patient who received topical vancomycin prophylaxis developed a deep infection. This difference was not significantly different.

Foot and Ankle

In a retrospective matched cohort study, 81 diabetic patients who underwent foot and ankle reconstruction surgery and received 0.5-1 gram of topical intra-wound vancomycin were matched to 81 similar patients who received only intravenous antibiotic prophylaxis. (72) There was a statistically significant reduction in deep surgical site infection of 73%, but no significant reduction in superficial infections.

Elbow

Finally, a retrospective study including 272 patients who underwent open release of post-traumatic elbow stiffness reported decreased post-operative infection with the addition of 1 gram of topical vancomycin compared to intravenous cefazolin alone. (73) There was a statistically lower rate of SSI for patients in the topical vancomycin group (0.0%) as compared to those in control group (6.5%).

Conclusions

Surgical guidelines recommend antibiotic prophylaxis in orthopaedic procedures, especially in cases with prosthesis implantation. Administration of local antibiotics in conjunction with parenteral antibiotics is attractive to surgeons seeking to reduce the incidence of SSI. However, there is only a single randomized trial in the orthopaedic literature that assessed the use of topical intra-wound antibiotics in spinal surgery, and few studies exist in other fields of orthopaedics. Future research should focus on providing high quality evidence that can help to define the role of local intra-wound antibiotics in orthopaedic surgery.

Competing Interests

The authors have declared that no competing interest exists.

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