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Review

Vancomycin-soaked wrapping of harvested hamstring tendons during anterior cruciate ligament reconstruction. A review of the 'vancomycin wrap'☆,☆☆

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ABSTRACT

The practice of 'vancomycin wrapping' of harvested hamstring autografts during Anterior Cruciate Ligament Reconstruction (ACLR) surgery has gathered recent interest.
This practice involves the wrapping of harvested grafts in a vancomycin-soaked swab during the preparatory phase. Different techniques are observed, and a small number of studies have shown that pre-soaking hamstring ACLR grafts in this manner dramatically reduces the post-surgical infection rate compared with standard intravenous antibiotic prophylaxis alone. However, the literature surrounding this practice is surprisingly limited and thus the basis and rationale of the 'vancomycin wrap' has established itself largely without question. The exact popularity of this practice is difficult to establish but there has been increasing disclosure of its efficacy in reducing post-operative infection in ACLR since 2012.
We provide a synopsis of the current literature surrounding vancomycin and its use in 'wraps' in ACLR to help apprise the surgeon of the nature of infection in ACLR, the rationale for vancomycin, whilst considering evidence to support alternatives and discussing potential ramifications for future practice.

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1. Introduction

Infection is the nemesis of the surgical world, of considerable concern in orthopaedic surgery. The use of systemic prophylactic antibiotics is legion to orthopaedic procedures, especially those concerning the insertion of metalwork, implants, or grafts [1], and has been standard practice for over 30 years [2,3].

Established infection prevention in Anterior Cruciate Ligament Reconstruction (ACLR) involves administering intravenous antibiotics [2,4]. However, the agent, delivery, timing and number of doses have a huge variation. This disparity is multifactorial; reflected in the literature, geographical microorganism prevalence, individual or unit experience and established protocols.

Described intravenous antibiotic administrations that have been shown to significantly reduce postoperative infection rates in knee surgery include at least 10 min before Tourniquet inflation, 15–120 min before skin incision, or 30–60 min before the start of the procedure [5–8].

Infection rates following ACL reconstruction are reported between 0.14 and 1.7%, and predominantly occur in the first four to six weeks postoperatively [9–11]. The two overwhelmingly prevalent organisms isolated are coagulase negative staphylococcus (62.5%) and *Staphylococcus aureus* (21.9%) [4,12,13]. Other commonly reported pathogens include Enterobacteriae, *Propionibacterium acnes*, and Pseudomonas [4,14]. However, as many as 75 different microorganisms have been identified in post-operative ACLR infection [12,13,15,16]. A greater incidence of postoperative infection using hamstring grafts compared with patella tendon bone grafts has been established [16–19].

The high prevalence of Coagulase negative staphylococcus in ACLR infection has led to the hypothesis that the most likely aetiology is graft contamination from the patient's own skin flora during harvesting and preparation [14,20,21]. Indeed, a 14–23% bacterial contamination rate during ACL autograft harvesting and manipulation alone during the preparation phase has been shown [13,14,22]. Despite this number, positive culture rates from hamstring grafts do not correlate to developing infection [23]. In the setting of the dropped hamstring graft this rises to 23–40% [13,24].

Predisposing factors to infection are varied and well recognised [14]. Specific to ACLR, the apparent failure of antibiotic intravenous prophylaxis is thought to be due to bacterial colonisation by skin commensals of a poorly vascularised hamstring tendon with levels of intravenous IV antibiotic below the minimum inhibitory concentration (MIC) [18].

Infection following ACLR can be devastating. Combined with the classical profiles of ACLR patients with observed trends in age, fitness, and high functional demands [25,26], developing any of these complications following infection after ACLR can be life changing and catastrophic. Complications including graft failure, potential graft removal, arthrofibrosis, cartilage loss, degenerative arthritis, osteomyelitis, and repeat surgery [27,28,30]. Psychosocial and socioeconomic costs are significant and should not be underplayed [21]. Cohorts of infected ACLR's compared with matched controls have longer recovery times, reduced initial activity scores and return to sports, although long term functional scores show no difference at 60 months postoperatively [29].

1.1. Management of infected ACLR

Early diagnosis and initiation of treatment is vital. In most cases, serial arthroscopic lavage, synovectomy, and appropriate IV antibiotics are the usual gold standard of treatment usually allowing for graft retention. Infection eradication is made difficult by factors including poor vascularity, reduced joint antibiotic penetration, and biofilm formation [20]. Deep infection may necessitate graft and hardware removal, and a second stage ACLR four to six months later [21]. There is widespread variation in the management of infected ACLRs. Attempts at disseminating management algorithms are described in the literature but presently management is unit or surgeon specific [20].

The constant battle against surgical infection necessitates innovation in maximising antibiotic efficacy to limit risk. An enterprising example of this lies in the 'vancomycin wrap' — first described by Vertullo et al. in 2012 [30]. Derivations exist but the principles are the same. The practice involves wrapping a swab around the ACL graft before placement in a tray or sterile plastic bag, into which vancomycin solution is added thus soaking the swab. All descriptions use a vancomycin concentration of 5 mg/ml. The graft is immersed for 10–15 min or until ready for implantation [4,20,21]. Prior to insertion, some advocate rinsing the graft with saline [20]. Emphasis is made on avoiding surgeon contact with the graft and avoiding contact between the vancomycin-soaked swab and the patients skin to prevent commensal exposure [20,21].

We present a review of the practice of vancomycin wrapping in ACL reconstruction, describing the background, evidence, effect on tissues and recommendations for further study.

1.2. Methodology

To provide a semblance of objectivity to articles reviewed regarding the use of the 'vancomycin wrap', a search for all clinical studies comparing the routine use of pre-operative IV antibiotics prophylaxis alongside vancomycin-soaked grafts intra-operatively was performed using MEDLINE and PUBMED databases up to July 2018. Studies of all levels of evidence amongst English language papers were included.

The terms: "(Anterior cruciate ligament Reconstruction) AND (infection AND prevention) OR (vancomycin) OR (tendon AND graft AND soaking) were used. Published conference abstracts were excluded. References of included studies were subsequently searched manually to identify missed articles. The search confirmed a paucity in articles — four papers in total concern vancomycin wrapping of harvested tendon in ACLR against standard pre-operative Intravenous antibiotic administration. This search also

produced five studies that considered alternatives to the 'vancomycin wrap' and describe techniques, differing antiseptic media, in combating the 'contaminated graft'. Similarly, terms using descriptions of vancomycin toxicity and biomechanical properties were searched using MEDLINE and PUBMED databases up to July 2018. Again, a paucity of articles was found, but 10 articles are described here with one article apiece describing bovine and porcine model effects.

1.3. Supporting studies for the efficacy of the 'vancomycin wrap'

A small number of clinical studies overwhelmingly indicate that pre-soaking grafts during ACLR can significantly reduce and even nullify postoperative infection when combined with traditional IV antibiotic administration.

Vertullo et al. first described the technique and efficacy of the vancomycin wrap in reducing infection in ACLR with hamstring grafts [30]. They reported a post-operative infection rate in four out of 285 patients (1.4%) who received intravenous antibiotics alone, and no infections in 870 patients (0%) who received IV antibiotics and an additional vancomycin soaked graft.

Phegan et al. also demonstrated the efficacy of the vancomycin wrap in reducing infection post-ACLR using hamstring autografts in a study of 1585 patients [20]. They showed a 0% infection rate in a prospective series of 1300 consecutive patients who had their harvested hamstring autograft 'wrapped' in vancomycin in addition to preoperative antibiotics, compared with 1.4% in a retrospective control group of 285 patients.

Similarly, Perez-Prieto et al. compared two groups undergoing ACLR that included both hamstring (84%) and bone-patellar tendon-bone (16%) graft reconstructions [4]. The first group ($n = 810$) received standard intravenous preoperative antibiotics, whilst the second group ($n = 734$) received vancomycin wrapping in addition. The first group had a postoperative infection rate of 1.85%, whilst the second group had 0% ($P < 0.001$). The reduction in infection was equal to both hamstring and BPTB groups.

In a follow-up study, the same author showed that vancomycin soaking fully eradicates contamination after harvesting and handling of hamstring autografts by comparing vancomycin soaked and control cultured graft samples taken at differing points of harvesting and preparation [14]. No growth was seen in the vancomycin-soaked group, whilst 14% of samples taken after harvesting without vancomycin soaking grew positive cultures. Ten percent of samples taken after preparation not soaked in vancomycin grew positive cultures.

1.4. Microbiology & rationale for vancomycin

Vancomycin was originally introduced in 1972 to counter Methicillin resistance in *Staphylococcus aureus* and coagulase negative staphylococci [31]. The rationale for its use in 'wrapping' in ACLR lies down to its pharmacokinetic properties that make it an ideal agent. These include low allergenicity, heat stability, safety for local use, and large volume of distribution. It has a bactericidal action against skin commensals such as *S. aureus* and coagulase negative staphylococci, which are the most common pathogens isolated in ACLR infection by far [4,12,13,15,16,20].

Vancomycin is currently used in many formats in orthopaedic surgery to good effect. Arthroplasty undertaken with bone cement containing heat stable vancomycin demonstrates reduced infection rates [32,33]. Titanium prosthetic implants covalently coated with vancomycin prevent bacterial adherence, proliferation, and formation of a biofilm by *Staphylococcus aureus*. [32]. The effective soaking of grafts and implants in antimicrobial solution to reduce infection rates has been employed in Plastic surgery [34], Urology [35], and Cardiothoracic surgery [36], all pre-dating the use of vancomycin wraps in ACLR. Topical vancomycin has been used in thoracic and spinal surgery to reduce deep infection for many years [21,35,38]. Vancomycin application to sternal wounds in addition to IV prophylaxis on patients undergoing coronary artery bypass grafting statistically reduces the incidence of post-operative wound infection [36]. These practices have not encountered any risk of resistance in over fifteen years of use [21,37,39,40].

1.5. Vancomycin toxicity and effect on tissues

Sparse evidence on toxicity of vancomycin on chondrocytes and tendons exists, with variability in studies regarding human or animal tissue, and in-vivo versus in-vitro evidence. A minimum of two milligrams per millilitre vancomycin concentration is required for effective eradication of staphylococcal species with at least five milligrams per millilitre required for the eradication of Staph. Epidermidis [20,41]. This two milligrams per millilitre concentration is lower than observed osteoblast and chondroblast toxicity concentrations [42] and allows for a wide therapeutic window that avoids local tissue toxicity [20]. Vancomycin has been shown to maintain its concentration for at least 24 h in pre-soaked bovine tendon [39]. Grayson et al. observed that tendon continues to elute vancomycin into the surrounding environment. Rinsing the tendon with saline affects the initial amount of vancomycin in the surrounding solution due to removal from the tendon surface but there is still elution of vancomycin following this, indicating a capability of tendon to act as a storage reservoir, with a correlation between increased tendon size and larger eluting effect. Therefore, the act of pre-soaking converts the graft from any source of potential contamination into an alternative prophylactic method against infection.

Vancomycin concentrations above 125 mg/ml are required before osteoblastic toxicity is seen and bone regeneration is inhibited in vitro [32], far exceeding the five milligrams per millilitre concentrations used in wrapping during ACLR [4,14,20,30]. However, Shaw et al. evaluated Porcine chondrocyte response to increasing concentrations of topical vancomycin, noting concentrations over five milligrams per millilitre or more had a statistically significant increase in chondrocyte death [25]. Little is known about the biomechanical effects of vancomycin on tendons. The only known study was performed by Schuttler in a porcine model [41]. No signs of biomechanical impairment of vancomycin wrapped flexor tendons was observed using concentrations ranging from one to 10 mg/ml.

1.6. Are there alternatives?

Whilst it is clear that vancomycin proves a highly effective topical agent against infection in ACLR, there is limited evidence that has evaluated antibiotic alternatives. Dogan et al. explored the effect of vancomycin, teicoplanin and linezolid on human chondrocytes, with no significant difference shown between any antibiotic. However, these results were not in vivo and the authors recommended further study [43].

Alternatives to vancomycin only emerge from the study of decontamination in the setting of the dropped ACL graft on the theatre floor, although they do not have the same efficacy when compared with vancomycin. Plante demonstrated a sterilising effect applying Bacitracin/chlorhexadine soaks to dropped ACL graft samples. Soaking of the dropped graft resulted in a three percent positive culture rate versus 23% in the control group. Of note, no correlation was found between the length of time grafts remained on the floor and positive culture [13]. Similarly, Badran showed soaking dropped hamstring grafts in either four percent chlorhexadine + bacitracin reduces graft contamination in excess tendon from hamstring autograft specimens and resulted in fewer positive cultures [22]. Barbier determined how effective various antiseptics were at decontaminating spare hamstring autograft dropped on the floor next to the surgical field. They showed the overall risk of infection to be 40% following a dropped graft but noted this potential infection rate could be reduced by immersing the graft in either four percent chlorhexidine gluconate solution or 10% povidone–iodine solution [24].

As with vancomycin, few studies have considered the potential adverse biochemical effects from these agents. Alomar et al. [44] investigated varying concentrations of chlorhexidine for adverse effects on collagen and tendon fibroblasts in ACL grafts. Four percent chlorhexidine treatment highlighted significantly less viable tendon fibrils and dissociated fibrils causing weakness and collagen breakdown. Lower concentrations also had cytotoxic effects on general cell viability.

1.7. Suggestions for further study

We believe this is the first review of its kind providing a synopsis of vancomycin soaking of harvested hamstring grafts in ACL reconstruction, whilst summarising the rationale and background. The studies discussed highlight a remarkable reduction of infection rates using the vancomycin 'wrap' in addition to standard intravenous antibiotic use [4,14,20,30]. It must be noted that despite a structured process to recruit all suitable articles on this subject there are indeed only a small number that qualifies. Furthermore, there is currently no data to establish the ubiquity of this practice amongst the knee community. Given that the Papers described in this article are from 2012 onwards [4,14,20,30], it is pertinent to bear in mind that the dissemination of new practices, especially with tangible and credible results does take time. Establishing the exact popularity of the 'vancomycin wrap' has advantages. Ascertaining the number and geographical proportions of those unacquainted with the practice also allows more focused dissemination of the practice and its evidence base thereafter. A wider audience awareness may increase the development of ideas and discussion in this area and facilitate much needed further research. Further considerations present themselves for study.

1.8. Other antibiotics

There are no comparative studies evaluating other antibiotic groups efficacy in 'wraps' in ACLR. Undeniably vancomycin has proven itself to be a highly effective agent [4,14,20,30], but other alternatives may exist that have similar efficacy that offer clinical and financial advantages. Other agents may show similar efficacy and would also reduce the likelihood of resistance faced with the use of vancomycin only.

There is paucity exploring vancomycin toxicity on human cells and tissues. From the reviewed literature, we can establish that vancomycin is safe for human chondrocyte and tendon in doses less than or equal to five milligrams per millilitre [41,45], However, given the observed eluting effect tendons have as reservoirs for vancomycin in bovine models, further study is needed to establish this in human tendon.

The biomechanical tolerance of porcine hamstring tendon with vancomycin has been established [41], but the effects upon human hamstring tendon with vancomycin or other agents remain unknown. Given the vital stability and function the ACL provides to the knee, further study is welcomed to establish biomechanical effects topical vancomycin or other agents may exert on human tendon and chondrocytes, both in ACLR and more generally.

2. Conclusion

The use of antibiotics in orthopaedic surgery has hugely improved patient outcomes, enabling us to perform procedures with the risk of small but acceptable infection rates. Indeed, the ability to perform safe surgery relies upon a reasoning that a procedure cannot be justified if it confers a high likelihood of complication and harm to the patient (unless life or limb threatening). Antibiotic use has changed the surgical landscape in this regard. Regarding ACLR, lower infection rates are seen in comparison with many other orthopaedic procedures [4] already, but the practice of 'vancomycin wrapping' serves to show that supplementation of existing antibiotic prophylaxis can achieve even more remarkable improvements [4,14,29,30].

However, this should not be taken for granted. The importance of simple theatre steps and etiquette cannot be overemphasised. Effective hand washing, gowning, patient preparation, hair removal, laminar flow, and staff movement [21,46] have always been the mainstay of reducing infection in modern surgery and always will be.

Whether the addition of the vancomycin wrap represents wise and judicious antibiotic is a matter for debate as we look forwards. There are significant challenges ahead as we concede the emergence of antibiotic resistance, which concerns a global audience [31]. We approach a nervous crossroad with resistance and the race for new developments.

Whilst the evidence supporting vancomycin wrapping is resounding, we have a shared responsibility to look beyond the patient on the table and consider future ones too. Multiple Antibiotic use in ACL reconstruction may cause significant future problems. Whilst the small number of discussed studies show significant results in negating postoperative infection, it may be a short-term success that expedites significant long-term problems with resistance. The emergence of vancomycin resistant genes in bovine enterococci secondary to Avoparcin use in cattle feed is established. Subsequent evidence of horizontal gene transfer to *S. aureus* and development of vancomycin resistant *S. aureus* should worry us all [47]. We should all be prepared for the challenges ahead whilst rationalising antibiotic use in the present.

Developing effective infection management algorithms, adherence to simple theatre precautions, and a collective recognition of the need for further study is paramount. Whilst the 'vancomycin wrap' has had a remarkable impact, we must remember over-reliance may expedite a reversal in fortunes sooner than we would like to admit. Orthopaedic Surgery has always been a beacon of constant innovation and improvement, but resistance is one of the greatest dangers we have yet to fully encounter and may render the vancomycin wrap obsolete quicker than we think.

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