



■ SPORTS & ARTHROSCOPY

Gentamicin pre-soaking of hamstring autografts decreases infection rates in anterior cruciate ligament reconstruction

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Aims

Graft infection following anterior cruciate ligament reconstruction (ACLR) may lead to septic arthritis requiring multiple irrigation and debridement procedures, staged revision operations, and prolonged courses of antibiotics. To our knowledge, there are no previous studies reporting on how gentamicin pre-soaking of hamstring grafts influences infection rates following ACLR. We set out to examine this in our study accordingly.

Methods

This retrospective study included 2,000 patients (1,156 males and 844 females) who underwent primary ACLR with hamstring autografts between 2007 to 2017. This included 1,063 patients who received pre-soaked saline hamstring grafts for ACLR followed by 937 patients who received pre-soaked gentamicin hamstring grafts for ACLR. All operative procedures were completed by a single surgeon using a standardized surgical technique. Medical notes were reviewed and data relating to the following outcomes recorded: postoperative infection, clinical progress, causative organisms, management received, and outcomes.

Results

Superficial wound infection developed in 14 patients (1.31 %) receiving pre-saline soaked hamstring grafts compared to 13 patients (1.38 %) receiving pre-gentamicin soaked hamstring grafts, and this finding was not statistically significant ($p = 0.692$). All superficial wound infections were treated with oral antibiotics with no further complications. There were no recorded cases of septic arthritis in patients receiving pre-gentamicin soaked grafts compared to nine patients (0.85%) receiving pre-saline soaked grafts, which was statistically significant ($p = 0.004$).

Conclusion

Pre-soaking hamstring autographs in gentamicin does not affect superficial infection rates but does reduce deep intra-articular infection rates compared to pre-soaking hamstring grafts in saline alone. These findings suggest that pre-soaking hamstring autografts in gentamicin provides an effective surgical technique for reducing intra-articular infection rates following ACLR.

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Introduction

The rates of anterior cruciate ligament reconstruction (ACLR) have increased 12-fold in England over the last two decades from 2.0/100,000 to 24.1/100,000.¹ This trend has potential to increase, as rates of surgical reconstruction remain lower than other countries, with international registry data suggesting that the rates of ACLR are 32/100,000 in Sweden and 28 to 52/100,000 in the USA.^{2,3}

Although ACLR has proven to be an effective method of restoring knee stability, the problem of deep infection following this procedure is a debilitating complication, which may subsequently require prolonged intravenous (IV) antibiotics, multiple reoperations for irrigation and debridement, graft removal, and staged revision reconstruction.^{4–7} Clinical outcomes following ACLR are adversely affected by infection, leading

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Table I. Patient demographics. All anterior cruciate ligament reconstruction procedures were performed from 2007 to 2011. No active smokers were operated on in either group.

Graft	Gentamicin/ 0.9% NaCl (n = 937)	0.9% NaCl (n = 1,063)	p-value
Sex, F:M	384:553	460:603	0.302*
Mean age, yrs (SD; range)	31.9 (11.7; 16.3 to 51.4)	30.2 (14.7; 16.2 to 61.6)	0.574†

*Chi-squared test

†Independent-samples t-test

to worse functional outcomes, development of early osteoarthritis, increased pain, and increased risk of graft failure.^{4,8,9}

Several studies have examined risk factors for deep infection following ACLR.^{8,10-12} It has been suggested that graft infection with skin flora is the main contributory factor in infection.⁴ Multiple studies have shown that pre-soaking grafts in vancomycin may lead to decreased deep infection rates.¹³⁻¹⁵ However, potential disadvantages of vancomycin include development of antibiotic-resistant organisms from overuse, graft toxicity, and increased cost compared to alternative agents.¹⁶ Current literature has not reported any increased laxity, re-rupture rates, or worse short- and mid-term functional outcomes with vancomycin use.¹⁴ Biomechanical studies have also not demonstrated any impairment of the hamstring autograft tendons following vancomycin soaking.^{17,18} More recently, studies have shown that gentamicin in the irrigation fluid may help to reduce the risk of joint infection after ACLR.^{19,20} However, to our knowledge, there are no existing studies reporting on how gentamicin pre-soaking of hamstring grafts influences infection rates following ACLR.

The objective of this study was to establish the effect of gentamicin pre-soaking of hamstring autografts on infection rates following ACLR. The hypothesis was that gentamicin pre-soaking of hamstring grafts would reduce infection rates following ACLR compared to pre-soaking hamstring grafts with saline alone.

Methods

This retrospective study included 2,000 patients (1,156 males and 844 females) who underwent primary ACLR with hamstring autografts between 2007 to 2017. Demographics are outlined in Table I. This included 1,063 patients who received pre-soaked saline hamstring grafts for ACLR (group 1) followed by 937 patients who received pre-soaked gentamicin hamstring grafts for ACLR (group 2). Exclusion criteria were as follows: patients with a history of ipsilateral septic arthritis; revision surgery; patients undergoing simultaneous procedures (i.e. osteotomy, meniscal repair, cartilage reconstruction, or other knee ligament reconstructions); patients with open procedures; and immunocompromised patients,

diabetes, steroid treatment, immunomodulator treatment, or a history of IV drug addiction or alcoholism. All operative procedures were completed by a single surgeon (FSH) using a standardized surgical technique. Medical notes were reviewed and data relating to the following outcomes recorded: postoperative infection, clinical progress, causative organisms, management received, and outcomes. All patients underwent local physiotherapy rehabilitation and were followed up remotely or in person at six weeks, one year, and two years after surgery. Outcomes and presentations to external institutions were recorded at this point. A total of 34 patients from the gentamicin group and 47 patients from the saline group were lost to follow-up between six weeks and two years. All study patients provided informed consent.

Surgical technique. All patients received 1.5 g IV cefuroxime 20 minutes prior to skin incision. 800 mg IV clindamycin was given to patients who had a documented cephalosporin allergy. In both groups, a quadrupled Gracilis-Semitendinosus hamstring tendon autograft was used for ACLR. The skin was prepared using a 2% Chlorohexidine gluconate solution delivered by a 26 ml "ChloraPrep" applicator (Becton Dickinson, Franklin Lakes, New Jersey, USA). After preparation and draping with tourniquet control, gracilis and semitendinosus tendons were harvested through a longitudinal incision over the tendons' insertion to the anteromedial aspect of the proximal tibia. An arthroscopic examination was performed with two standard arthroscopic portals. After harvest the graft was soaked in gentamicin solution prior to preparation to ensure adequate exposure time. In the saline group, the four-strand gracilis and semitendinosus autografts were wrapped in large swabs soaked in 0.9% NaCl solution. In the gentamicin group, grafts were wrapped in large swabs soaked in 80 mg of gentamicin diluted in 100 ml of 0.9% NaCl solution, giving a gentamicin concentration of 0.8 mg/ml. For each case the femoral tunnel was drilled as the graft was prepared – in this way surgical time was not influenced by graft soaking. Grafts remained wrapped for a minimum of 15 minutes while the arthroscopic stage of the procedure was performed. The knee was irrigated with a sterile saline solution throughout transplantation. Grafts were fixed with Endobutton (Smith and Nephew, Memphis, Tennessee, USA) and Interfix (DePuy Synthes, Warsaw, Indiana, USA) implants on the femur and tibia, respectively. Port sites were closed with a single layer 3/0 nylon suture. Larger incisions were closed in layers with the outer layer closed with a 3/0 absorbable monofilament (Monocryl; Ethicon, Bridgewater, New Jersey, USA). No postoperative IV antibiotics were given. In order to minimize any potential local irritation or dermatitis, the skin was washed with a saline solution and dried prior to dressing application.

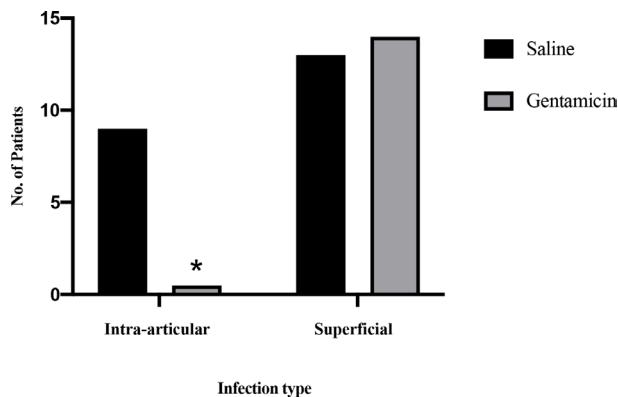


Fig. 1

Intra-articular and superficial infections post anterior cruciate ligament reconstruction. *There was a significantly higher rate of intra-articular infection in the saline group compared to the gentamicin group ($p = 0.004$, chi-squared test).

Statistical analysis. Descriptive statistics including mean, range, and SD were calculated for all recorded variables. Differences in complications between the two groups were tested by chi-squared test and Fisher's exact test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (v.24, IBM, Armonk, New York, USA) and GraphPad Prism v.9 (GraphPad Software, San Diego, California, USA)

Intra-articular infection diagnosis. Patients presenting with fever, increasing knee pain, effusion, tenderness, or decrease in knee range of motion were admitted to the hospital and investigated. Full blood cell count, CRP, and ESR were obtained. Aspiration was performed if the above clinical features were present. Septic arthritis diagnosed on the basis of one of the following diagnostic criteria or at least two highly suspicious parameters being present, as described by Yazdi et al.¹⁹ Diagnostic criteria: positive culture or positive Gram stain; purulent aspect of the aspirate; polymorphonuclear cell percentage $> 90\%$; cell count $> 100,000$. Highly suspicious parameters: turbid appearance; polymorphonuclear cell percentage from 75% to 90%; cell count from 20,000 to 100,000; glucose $< 50\%$ serum level; CRP value $> 150 \text{ mg/dl}$ day 3 post op, or $> 20 \text{ mg/dl}$ day 15 post op.

Results

Intra-articular infections. The overall rate of intra-articular infection was 0.45%. All cases of septic arthritis developed within the first four weeks postoperatively. As all infections presented within the first four weeks, analysis was based on follow-up at the six-week review. There was a significantly higher rate of intra-articular infections in the saline group compared to the gentamicin group (9/1,063 vs 0/937; $p = 0.004$, chi-squared test) (Figure 1). The absolute risk reduction was 0.85% (confidence interval (CI) 0.3% to 0.4%) in the

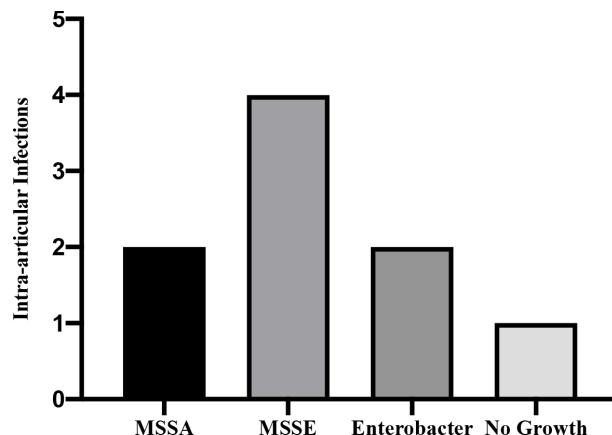


Fig. 2

Cases of intraarticular infection by species. Six of the nine cases of septic arthritis grew a *Staphylococcus* species. Two cases grew methicillin-sensitive *Staphylococcus aureus* (MSSA), four cases grew methicillin-sensitive *Staphylococcus epidermidis* (MSSE), two cases grew an enterobacter species, and one case was a negative culture.

gentamicin group compared to the saline group. The number needed to treat (NNT) is 119 (CI 71.6 to 338.0) in the gentamicin group. Six of the nine cases of septic arthritis grew a *Staphylococcus* species. Two cases grew methicillin-sensitive *Staphylococcus aureus* (MSSA), four cases grew methicillin-sensitive *Staphylococcus epidermidis* (MSSE), two cases grew an enterobacter species, and one case was a negative culture. Figure 2 outlines the distribution of pathogenic organisms. Eight of the cases were resolved with arthroscopic washout and treatment with IV antibiotics. Of these four cases resolved with a single washout and IV antibiotics, four cases required a repeat washout procedure. One case was revised in a staged procedure to an allograft due to persistent infection despite IV antibiotic treatment.

Superficial infections. The overall rate of superficial infection was 1.3%. No difference was identified between the saline and gentamicin groups (13/1,063 vs 14/937; $p = 0.69$) (Figure 2).

Complications. There were five cases of deep vein thrombosis (DVT) and one case of pulmonary embolism (PE) in the patient cohort giving a DVT/PE rate of 0.3%. Although there were more DVT/PEs in the saline group compared to the gentamicin group (4/1,063 vs 2/937) this was not statistically significant ($p = 0.694$, chi-squared test). In our cohort no local allergic responses were recorded.

Discussion

The findings of this study support the hypothesis that gentamicin pre-soaking of hamstring autografts reduces deep intra-articular infection rates compared to saline pre-soaking of hamstring autografts following ACLR. There was no difference in the superficial infection rates between the two treatment groups. The most

common causative organism for deep infection was MSSA. Patients were treated with arthroscopic irrigation and a course of IV antimicrobials.

Gentamicin is an aminoglycoside antibiotic, which works by binding to the 30s subunit of the bacterial ribosome and thereby inhibiting bacterial protein synthesis. It requires a short contact time to produce the desired inhibitory effect which is beneficial in the operative setting. In addition, the solutions are quick and easy to prepare. Gentamicin is active against a wide range of bacterial infections; while it is primarily effective against Gram-negative species, it is also effective against Gram-positive species.²¹⁻²⁴ In particular, it has been shown to be effective in decolonizing *Staphylococcus aureus* from inoculated open fractures.²⁵ It is most effective against rapidly multiplying bacteria including skin commensals such as *S. Aureus* and coagulase-negative staphylococcal species; these are the most common casual organisms in septic arthritis post ACLR.^{4,26,27} Offerhaus et al¹⁴ reported that, of 22 infections, 16 (73%) were attributed to coagulase-negative *Staphylococcus*, and two cases (9%) resulted from *S. aureus*. Similar causal organisms were identified in our study six cases growing a *Staphylococcus* species. Enterobacter species were also grown in our study, which are readily treatable with gentamicin.^{28,29} The prevalence of skin commensal infective organisms in our study is suggestive of direct skin to graft contamination as noted by Judd et al⁴, which highlights the importance of keeping contact of the graft with the skin to a minimum.

While deep infection following ACLR is a devastating complication with high morbidity, there is a paucity of literature examining preventative strategies to limit postoperative infection.^{4,30,31} Baron et al¹³ observed a reduction in infection post-ACLR from 1.2% to 0.1% in a retrospective analysis of 1,640 patients with the use of vancomycin-soaked grafts. Similar studies by Vertullo et al³² and Perez-Prieto et al³³ reported reductions in post-operative infection from 1.4% to 0% and from 1.9% to 0%, respectively. In studying 1,779 patients with a 28-month follow-up Offerhaus et al¹⁴ noted a reduction of deep infection rate from 2.4% to 0%. While the benefits of vancomycin soaking have been well documented, concerns have been raised over the development of resistance, cost, and lack of alternatives in the case of allergy.¹⁶ Our results suggest that pre-soaking with gentamicin achieves comparable reductions in infection rates and may offer a cheaper and more readily available alternative.

Like vancomycin, gentamicin demonstrates low chondrotoxicity compared to other antibiotics and is considered safe for intra-articular administration.^{34,35} Vancomycin is associated with a vast number of hypersensitivity reactions; cross reactivity has been

reported the beta-lactam antibiotic class in up to 15% of patients.²⁸ However, allergic hypersensitivity reactions from aminoglycosides are reported in < 2% of patients.³⁶ Contact dermatitis from topical aminoglycoside use is the most frequently reported reaction with aminoglycosides.^{37,38} In our cohort no systemic or local allergic responses were recorded prior to discharge or at six weeks follow-up. Thorough saline irrigation of the skin post procedure may account for the absence of chemical irritations noted in our study.

A significant risk with the routine use of antibiotics is a change in the resistance profile. The literature has not established whether the risk of antibiotic resistance is increased in ACL surgery with the administration of any intra-articular antimicrobial agent. Single-dose local antibiotics have not produced any increased risk of resistance with vancomycin when used as prophylaxis in thoracic and spinal surgery.^{39,40} The normal variance in resistance profile over time and between institutions must be taken into account when examining this. Ghobrial et al⁴¹ did report an increase in cultured Gram-negative or polymicrobial infections where powdered local wound vancomycin had been used as prophylaxis for posterior spinal fusions. No studies, to our knowledge, have been conducted examining the resistance profiles pathogens of gentamicin for surgical prophylaxis alone. Resistance development with the use of gentamicin-impregnated bone cement in primary arthroplasty results in the literature are contradictory. Hope et al⁴² reported that the number of periprosthetic joint infection (PJI) cases caused by gentamicin-resistant coagulase-negative *Staphylococci* increased with the use of antibiotic-loaded bone cement, with gentamicin resistance found in 30% of 91 PJI cases. In an analysis of over 173 cases of infected primary arthroplasties implanted with antibiotic-impregnated bone cement, Hansen et al⁴³ did not find any increase in resistance in organisms cultured. While our numbers were low, no gentamicin-resistant pathogens were cultured, which suggests that resistance may not be common when gentamicin is used for local surgical prophylaxis in ACLR.

This study has multiple limitations. It is retrospective in nature and variables such as tourniquet time, length of stay, and surgery duration were not recorded. There is a potential temporal bias in that patients in the gentamicin group received surgery later in the study. Other areas in their preoperative and postoperative care, as well as improved surgeon performance based on gained surgical experience, may have contributed to a decreased risk of infection. The surgical technique varied slightly between the two groups in that a higher number of lateral extra-articular tenodeses were performed in the gentamicin group. Late presenting infections, as well as patients who may have presented to other institutions, may have been missed. While we

did not perform propensity score matching for comorbidities, the vast majority of the patient cohort were young, healthy individuals. We believe that the large number of consecutive patients in this study would negate any heterogeneity.

In conclusion, pre-soaking hamstring autografts in gentamicin does not affect the rate of superficial infections but does reduce deep intra-articular infection rates compared to pre-soaking hamstring grafts in saline alone. These findings suggest that pre-soaking hamstring autographs in gentamicin provides a simple and effective surgical technique for reducing intra-articular infection rates following ACLR.

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- B. Kayani: Edited the manuscript
- C. Wallace: Edited the manuscript
- R. Plastow: Edited the manuscript.
- F. S. Haddad: Conceptualized the study, Edited the manuscript

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