RESEARCH ARTICLE

The Effect of Gentamycin in the Irrigating Solution to Prevent Joint Infection after Anterior Cruciate Ligament (ACL) Reconstruction

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Abstract

Background: Arthroscopic reconstruction of ACL is an effective method to restore knee stability after ACL rupture. Postoperative septic arthritis (SA) is very uncommon while the incidence of serious complications range between 0.14% and 1.8%. Some of the devastating consequences of septic arthritis can encompass hyaline cartilage damage, arthrofibrosis, and in rare cases amputation. The purpose of this study was to evaluate the effect of gentamicin irrigation solutions as a process to restrain septic arthritis following arthroscopic ACL reconstruction.

Methods: In this retrospective cohort study, 1464 patients who underwent ACL reconstruction with hamstring tendon autograft in our institution over 7 years (February 2008 to January 2015) were included. The patients were divided into two groups based on the type of intra-articular irrigation solution used during the surgery. Patients in Group 1 (Saline) received intra-articular irrigation with normal saline (0.9 % sodium chloride) solution, while those in Group 2 (Gentamycin) received intra-articular irrigation with gentamicin (80 mg/L) added to the normal saline solution. Data about postoperative infection, its course, management, and outcome were obtained from patients' records.

Results: Seven patients developed SA, four of whom were from SALINE group (2.2%) and three from Gentamycin group (0.23%). The incidence rate of SA after arthroscopic ACL reconstruction was significantly lower ($P < 0.05$) when irrigated with gentamicin solution than merely with saline solution.

Conclusion: Gentamicin irrigation solution has a preservative and protective effect against SA development following arthroscopic ACL reconstruction. We recommend evaluating this technique as a way in order to depreciate the prevalence of SA after ACL reconstruction.

Level of evidence: III

Keywords: ACL reconstruction, Gentamicin, Irrigating solution, Septic arthritis

Introduction

The anterior cruciate ligament (ACL) is regarded as the most reported prevalent ligament injured in the US, annually reporting between 100.000 and 200.000 ruptures (1-3). Thus, ACL reconstruction (ACLR) is a highly frequent practice that is expected to gain more popularity in the upcoming years (1, 3, 4).

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Septic arthritis (SA) after ACLR is although unfamiliar, it is potentially devastating post-operative complication (5). The reported occurrence rate fluctuates between 0.14% and 1.8% (6-8). The commonly reported predisposing factors implicated in developing SA after an ACLR are age, BMI, diabetes, smoking, previous or simultaneous surgeries, prolonged operation time, long tourniquet inflation time, drain application, and graft choice (9, 10).

Although prophylactic intravenous (IV) antibiotic is a standard practice, sometimes it might not be ample in hindering this post-operative complication (11). The reason for above theory is that the tendon graft has a poor blood supply. The result is lower antibiotic concentrations than the minimum inhibitory concentration, through which the tendon is prone to bacterial colonization by the skin flora when harvested (11).

Considering the pathogens included in SA post ACLR, *Staphylococci* is considered as the most widespread pathogen, accountable for approximately 90% of the cases, more than half of which are due to coagulase-negative *Staphylococci* (CNS) (6, 12, 13). Other pathogens involved are Propionibacteriumand Enterobacter species (13). Some authors have linked the high percentage of CNS to patients' skin-flora contamination during the graft harvest (14).

The literature presents abroad range on the incidence of SA post ACLR. Indelli et al. reported an occurrence of 0.14% in a series of 3500 consecutive ACLR cases (15). On the other hand, an incidence of 1.8% was reported by Torres-Claramunt et al.in a study with 810 consecutive ACLR (8, 11, 15-24). Schollin-Borg et al. recounted an incidence of 1.7% in a study with 575 ACLR (5).

Although occurrence of SA is not high, without appropriate management, it can lead to devastating outcomes with a serious impact on the patients' quality of life (25, 26). That is the reason of the significance to prevent, recognize and treat SA immediately as effectively as is possible.

Although prophylactic antibiotic irrigation solutions are used during orthopedic surgeries, however, there are still some inconclusive scientific evidence regarding its efficacy (6, 11, 12, 14-17, 19-24, 27-29). Gentamicin is a broad spectrum antibiotic effective against *Staphylococci*, gram-negative pathogens, *Pseudomonas* and others pathogens with a safe profile, is thermo-stable, as well as cost-effective (21, 29). Regarding these attributes, gentamicin is an appropriate option for intraoperative lavage during ACLR.

The purpose of this study was to investigate the effect of intra-operative gentamicin irrigation solution compared to saline in relation to the incidence of septic arthritis after arthroscopic ACLR. We hypothesized that gentamicin irrigation solutions would reduce postoperative infection rate after arthroscopic ACL reconstruction.

Materials and Methods

Following institutional review board (IRB) approval, single-institution chart reviews were queried to identify 1556 patients undergoing ACLR from Feb. 2008 to Jan. 2015 retrospectively.

Patients were classified in two groups. Group 1 (Saline) included patients who underwent ACL reconstruction with a hamstring tendon autograft, received preoperative IV antibiotics (Cefazolin, 1 gr), and intra-articular irrigation with normal saline solution (0.9 % sodium chloride) during surgery. Group 2 (Gentamycin) included patients who underwent ACL reconstruction with a hamstring autograft, received preoperative IV antibiotics (Cefazolin, 1 gr), and intra-articular irrigation with gentamicin (80 mg/L) added to the normal saline solution (0.9 % sodium chloride) during surgery.

Patients records were inspected, and data on preoperative evaluation, surgical procedure, follow up course, incidence of postoperative septic arthritis, its course, management, and outcome were collected and used for analysis.

Patients who required a simultaneous partial meniscectomy were included in the study. Exclusion criteria were considered as: 1) patients who had a history of chronic infection near the same knee, 2) those who had previously undergone ACL reconstruction and required revision, 3) those who required simultaneous osteotomy, meniscal repair, cartilage reconstruction, or other knee ligament reconstructions, 4) those who had open procedures, and 5) patients with IV drug addiction, alcoholism, steroid use, diabetes or immune deficiency.

According to the institution protocol, all patients were screened preoperatively for local or remote skin scratches or lesions. If any of these pathologies were present, the surgery was postponed until the lesion or infection improved. All surgeries were done by the same senior surgeon with the same protocol for preparation, draping, equipment, and surgical techniques.

The institution protocol for preoperative IV antibiotic is a dosage of Cephazolin (1 g) 30 min before inci¬sion. In case of allergy to the cephalosporin, vancomycin (1 g) or clindamycin (600 mg) was administered. There was not any report for allergy to cephalosporin in this study and all patients received Cefazolin (1 g) preoperatively.

In both groups, a quadrupled *Gracilis–Semitendinosus* hamstring tendon autograft was used for ACL reconstruction. 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, followed by anatomic reconstruction using the trans-portal technique. In all patients, the graft was fixed using Endobutton (Flipptack, Karl Storz, Tuttlingen, Germany) on the femoral side, and a bioabsorbable screw (Megafix screw, Karl Storz, Tuttlingen, Germany) on the tibial side.

For group one, normal saline in 3-L bags without any additives was used for irrigation. For group two, 240mg of gentamicin was added to the normal saline solution 3L-bags in order to have an 80 mg/L concentration. The reported minimum effective irrigating dose of

gentamicin is 50 mg/L(17). Therefore 80 mg/L was regarded as effective. The operation time fluctuated between 45-70 minutes, and 3-4 liters of solution was used for irrigation per surgery.

Based on SIGN (Scottish Intercollegiate Guidelines Network) and ASHP (American Society of Health-System) therapeutic guidelines postoperative antibiotics (cephazolin 1gr q6h) were administered for 24 h in both groups. Intra–articular drains were used for 24 h.

After operation, the patients were followed at weeks 1, 3, 6, 12, and 24. The same postoperative rehabilitation program was used for all patients and they were all advised to inform the surgeon in case of fever, joint swelling, increased pain, or limited ROM at any time during the follow up period. All patients were followed at least for 6 months.

Patients who experienced fever, severe knee pain, swelling, effusion, tenderness, or abrupt restricted motion in the knee were admitted to the hospital to check their blood cell count (WBC) with differentiation, C-reactive protein (CRP) titer, and erythrocyte sedimentation rate (ESR). The involved knees were aspirated and the aspirates were sent to the laboratory for diagnose. One diagnostic parameter or at least two highly suspicious parameters are diagnostic of septic arthritis after ACLR.

1. Diagnostic
– Positive culture or positive Gram
– Purulent aspect of the aspirate
– Polymorphonuclear cell percentage >90 %
– Cell count >100,000
2. Highly suspicious
– Turbid aspect
– Polymorphonuclear cell percentage; from 75 % to 90 %
– Cell count; from 20,000 to 100,000
– Glucose: <50 % serum level
– CRP value; >150 mg/dl day 3, or >20 mg/dl day 15 (30).

The statistical analysis of the study was conducted using the $\chi 2$ test with Yates correction and the Fisher exact test. A *P-value* of <0.05 was considered statistically significant.

All procedures involving human participants were performed based on the 1964 Helsinki declaration and its later amendments

Results

1556 patients were included in this study with the participitation of 180 patients in Saline group and 1376 patients in Gentamycin group. 3 patients from Saline group and 89 patients from Gentamycin group were excluded due to the loss of follow-up. Thus, at the end the study, a total number of 1464 patients were evaluated. The patients' characteristics in the two groups are shown in Table 1.

The mean follow up was 33.7 months (range 12-83 months). The mean age of Saline group and Gentamicin group was 27.2±2.49 years and 25.75±3.04 years, respectively. A total of seven postoperative septic arthritis cases were documented in both groups through the follow-up period (incidence: 0.4 %); four of them were reported in Saline group, giving an incidence of 2.2%, diagnosed 1-8 weeks after the surgery. Three SA cases were reported in Gentamycin group, giving an incidence of 0.23%, and diagnosed 2-8 weeks after the surgery. The average time for the presentation of symptoms after the surgery was 24.7 days (range 8–57 days).

All four patients who developed SA in Saline group were men with a mean age of 25.5 years at the time of the surgery (ranging 21–31 years). They presented with knee pain, effusion, and abrupt restricted range of motion. Two of them had low fever (T≤ 38 °C), one suffered from high fever (T> 38 °C) with chills and one did not have temperature changes. Table 2 indicates the characteristics of the reported postoperative SA cases in this group. Initially, the knees were aseptically aspirated and the aspirates were sent to the laboratory for further analysis. In addition, blood samples were collected for WBC count and ESR and CRP measuring. Every patient experienced straightaway arthroscopic irrigation and lavage, and synovial fluid, and tissue biopsy was sent for aerobic and anaerobic cultures. None of the autogenous ACL grafts appeared damaged at the time of arthroscopy. Thus all were kept. Immediately after the surgery, empirical intravenous antibiotic administration (Cefazolin and Gentamicin) was started. Later, there was an adjustment of antibiotic regimen based on clinical response and culture results. IV antibiotic therapy was prolonged for 1–2 weeks based on CRP titer, followed by oral antibiotic therapy for an additional 2 weeks. As soon as the patient was capable of tolerating to prevent arthrofibrosis, knee ROM and rehabilitation exercises were initiated. Also the patients were followed up with clinical examinations, WBC count and ESR and CRP measurements until they all returned in to their normal condition. As three months passed, all patients had full ROM, good stability, and no signs and symptoms for current or return of infection.

In Gentamycin group, three cases of postoperative deep infection were validated, all presented with knee pain, effusion, and limited range of motion, yet no fever. The characteristics of reported postoperative SA cases in this group are shown in Table 3.

The same protocol of management followed as it was

Table 1. The patients' characteristics in the two groups

	Number of patients	Males	Males%	Females	Females%	Mean age at surgery
Saline group	177	152	85.9%	25	14.1%	27.2
Gentamicin group	1,287	1,109	86.2%	178	13.8%	25.75

Table 2. the characteristics of reported postoperative SA cases in the Saline group

Case	Age	Sex	Prior knee surgery	Time from ACLR to diagnosis of infection	Lab data (blood) at the time of diagnosis	Joint fluid aspirate data	Culture (intra operative biopsy and joint aspirate)	Number of procedure after infection	Hospital stay (days)
1	31	M	None	20	WBC: 8,400 Poly: 70% ESR: 33 CRP: 82	Turbid yellow WBC: 19,000 Poly: 95%	Neg	3	13
2	21	M	Exostosis resection	8	WBC: 10,300 Poly: 73% ESR: 62 CRP: 130	Cloudy yellow WBC: 25,000 Poly: 80%	Neg	2	8
3	27	M	None	14	WBC: 6,300 Poly: 70% ESR: 76 CRP: 102	Turbid yellow WBC: 64,000 Poly : 85%	Pseudomonas	3	12
4	23	M	None	57	WBC: 13,200 Poly: 78% ESR: 76 CRP: 152	Very turbid yellow WBC: 36,600 Poly : 98%	Neg	3	14

Table 3. the characteristics of reported postoperative SA cases in the Gentamycin group

Case	Age	Sex	Prior knee surgery	Days from ACLR to diagnosis of infection	Lab data (blood) at the time of diagnosis	Joint fluid aspirate data	Culture (intra operative biopsy and joint aspirate)	Number of procedure after infection	Hospital stay (days)
1	27	M	None	28	WBC: 11,100 Poly: 80% ESR: 110 CRP: 83	Turbid yellow WBC: 85,000 Poly: 98%	coagulase-negative, S. epidermidis	4	30
2	27	M	None	32	WBC: 10,500 Poly: 70.5% ESR: 10 CRP: 1+	Cloudy yellow WBC: 15,600 Poly: 95%	Negative	1	10
3	31	M	None	21	WBC: 8,300 Poly: 75% ESR: 46 CRP: 35	Turbid yellow WBC: 87,000 Poly : 95%	Negative	2	13

previously described. Patients were exposed to instant arthroscopic irrigation and lavage, with extensive debridement of the necrotic and inflamed synovial tissue whenever it was required. Antibiotic therapy was prolonged for 4 weeks until the CRP titer were back to normal.

The first patient was a 27-year-old male who referred to another clinic, 4 weeks after surgery with knee pain, effusion, and limited range of motion, but no fever. The treating physician started oral antibiotics course for a period of 18 days although there was no sign of any clinical improvement, after which the patient was sent back to our clinic. At the time he presented to our clinic, his laboratory studies showed a peripheral white cell count of 11,100/μL with 80% PMN. ESR was markedly elevated (110 mm) and CRP was moderately increased (83 mg/L). The knee aspirate was turbid with a WBC count of 85,000/μL and 98% polymorphonuclear cells. The result of the culture identified coagulase-negative *S. epidermidis*. The bacteria were resistant to penicillin and amoxicillin, even though sensitive to gentamicin, methicillin, and vancomycin. The patient underwent arthroscopic debridement surgery during which the endobutton and the absorbable screw were removed. Three additional lavage and debridement surgeries were needed before achieving clinical improvements. The treatment continued with IV antibiotic therapy for 4 weeks until the CRP titer were back to normal. The patient's hospital stay lasted 30 days and the end of the follow up successfully treated the infection treated, although the patient had painful and limited ROM.

The second patient was a 27-year-old male, who referred the clinic 8 weeks after the surgery with knee pain, effusion and decreased range of motion, without fever. His laboratory studies showed a peripheral white cell count of 10500/μL with 70.5 % PMN. ESR was 10 mm and quantitative CRP was reported one plus positive. The synovial fluid aspirate was turbid with a white blood cell count of 15600/μL and 95 % polymorphonuclear cells. The results of the cultures were negative. The patient underwent open debridement surgery. The endobutton and the absorbable screw were found to be stable and were retained. Antibiotic therapy (IV and oral) continued for a period of 4 weeks until the CRP titer got back to its normal condition. He then achieved a painless full range of motion after the treatment of the infection.

The third patient was a 31-year-old man returning to our clinic 3 weeks after the ACL reconstruction with pain and limited ROM. ESR was 46 mm and CRP was 35mg/l. The knee aspirate was turbid, the white blood cell count of the aspirate was 87000/μL with 95% polymorphonuclear cells, and the results of the cultures were negative. Arthroscopic lavage and debridement was done and intravenous antibiotic was given to the patient for 10 days followed by oral antibiotics for 4 weeks, the result of which was a successful infection treatment without any complication.

Statistical analysis revealed that the rate of septic arthritis in gentamicin irrigation solution group was significantly lower than saline irrigation solution group (*P=0.012*).

Discussion

The most pivotal finding of this study was the incidence rate of SA after arthroscopic ACL reconstruction, which was significantly lower (*P<0.05*) when irrigated with gentamicin solution than with only saline solution. This study is capable of demonstrating the notion that Gentamicin irrigation solution has a protective effect against SA development after arthroscopic ACL reconstruction. In this retrospective cohort study on 1464 patients, who had ACL reconstruction with hamstring autograft, a total of 7 patients developed SA, including four patients from SALINE group (2.2%) and three from Gentamicin group (0.23%).

The primary cause of knee joint empyema is surgical interventions; in case of improper treatment can ultimately result in rapid joint destruction (31). There have been many potential complexities pinpointed to impress the clinical outcome after ACL reconstruction; among which septic arthritis has the most devastating consequences (31). Whilst proper functional consequences can be accomplished with early diagnosis and prompt management, full return to athletic activities cannot always be expected (30). Even though, the incidence of SA after ACLR is low (range 0.14–1.8 %), its consequences relinquish a severe challenge in clinical practice (22, 31).

Contamination of the graft is commonly associated with patient's skin flora, which might occur during harvest or even when it is introduced into the knee through the arthroscopic portals (14). That explains the higher infection rate with hamstring autografts (20). Plante et al. found contamination in 23% of hamstring tendone autografts (32).

Numerous clinical studies have demonstrated that majority of infections occur within the first month after surgery (31). Williams et al. in a series of seven patients claimed that the average time for septic arthritis diagnosis after ACL reconstruction is 21 days (33). Indelli et al. reported presentation between 9 and 34 days (15). McAllister et al. reported between 8 and 18 days, while other studies reported between 2 and 45 days (19, 22, 34, 35). In the present study, seven cases with postoperative SA were reported, six of which were diagnosed in the acute phase. Consistently with reports from other studies, the most common presentation was sudden knee pain, effusion, and limited range of motion; however, fever was recognized only in one of the patients (24, 36).

Little has been reported about the prevention of SA following an ACLR. Usual precautions practiced to avoid this complication are using prophylactic antibiotic before surgery and limiting hair removal (37, 38).

Antibiotics opted for surgical prophylaxis ought to cover microorganisms that usually are the main causes of infection, have an approved spectrum of side effects, be fairly inexpensive, and not readily lead to microbial resistance (18). In spite of being effective in other surgical fields, intravenous antibiotic prophylaxis commonly faces wit failure to hinder septic arthritis after ACLR due to poor vascularity of hamstring tendon autograft and its low levels below the required minimum inhibitory concentration (11). In our study, we found 2.2% postoperative infection rate in the Saline group, which was significantly higher than the Gentamycin group, and also was higher than infection rate reported

in the previous studies (5, 39).

Topical antibiotics were utilized in other areas of surgery, which have demonstrated a reduction in infection rates (40). Total joint arthroplasty undertaken with bone cement containing a heat stable antibiotic has presented a reduced rate of infection post-operatively (9, 23, 40). Also gentamicin lavage solution has been used over a long period of time in open fractures and total joint replacements to diminish the infection rate (21, 29). Bortnem et al have studied the therapeutic efficacy, cost, and safety of gentamicin prophylactic lavage solution in orthopedic surgery. They found out that gentamicin is a cost-effective antibiotic for intraoperative lavage, while its efficacy couldn't be proved in their study (17).

In other studies investigating local antibiotic prophylaxis in ACLR, Vancomycin received the most pivotal attention (31). Christopher J. Vertullo et al. studied 1,135 hamstring autograft ACL reconstructions, and compared two groups of patients who underwent ACL reconstruction with hamstring autografts with and without presoaking in vancomycin solution. Their outcomes revealed that the prophylactic vancomycin presoaking of hamstring autografts statistically decreased the rate of infection (41). Further, it was reported by Phegan et al. that using vancomycin solution to soak the graft reduced the infection rates after ACL reconstruction with either hamstring or patellar tendon autografts to zero, as it is contrasted with a control group showing an incidence of 1.85% in spite of the consumption of prophylactic IV antibiotics (36).

In this study, the incidence rate of septic arthritis following an ACLR was 0.23% in Gentamycin group, which is comparable to the lowest infection rate after ACLR in other studies (15). To the best of our knowledge, no other study reported on the role of intraoperative gentamicin irrigating solution in SA prevention after hamstring autograft ACLR.

Gentamicin is not only an inexpensive but also a worldwide available antibiotic with a broad–spectrum impact on the majority of gram-positive and gram-negative bacteria (42). On the other hand, Vancomycin is mainly active against gram-positive microorganisms and can't beat the affordability of gentamicin (31). Based on these merits, we were encouraged to claim that gentamicin seemed to be a more appropriate option than vancomycin for SA prophylaxis in ACLR. Moreover, the emergence of resistance to the third generation cephalosporin is more frequent when compared to amino-glycosides, based on which gentamicin is considered a better option when compared to cephalosporin, too (28).

Although the therapeutic index of amino-glycosides is narrow, using a low dosage of gentamicin as a lavage solution for a limited period of time (45–70 min) lowers the possibility of side effects occurrences (1). None of the evaluated patients had renal problems, and we suggest studying the effect of gentamicin irrigation on renal function to further justify its safety.

Previous knee surgery or concomitant surgical procedures performed during initial ACL reconstruction were reported to be a risk factor for septic knee arthritis either due to increased operative time, additional or larger incisions, lengthy tourniquet inflation or the use of suture material that acts as a foreign body (31). Using gentamicin irrigation solution in these circumstances might assist to decrease the postoperative infection rate.

There were some limitations in carrying out the present study. First, the possible toxic effect of gentamicin on human cartilage based on dosage and exposure time was not evaluated, and therefore in this respect, more studies are needed. Second, the exact diagnostic criteria to diagnose acute versus late infections has not been well defined in the literature. In this study, we used the same criteria for all cases. Third, we were not be able to find the effect of some variables like age, gender, BMI, CCI, operation time, tourniquet time and smoking as possible risk factors. Another study with logistic regression analysis is needed to evaluate the possible effects. Forth, in this study the rate of infection in saline group is much higher than reported in the literature. We did not find any reason for this difference. It may be because of less standard cares in our hospital. Fifth, the number of controls was much less than cases and we were not able to do matching. From many years ago, we stopped any arthroscopic ACLR without adding Gentamicin in the irrigation solution. Thus, the number of available control group was low in this retrospective study.

Gentamicin irrigation solution may have a protective effect against SA after arthroscopic ACL reconstruction. We suggest evaluating this technique as a mean to diminish the incidence of SA after ACL reconstruction.

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