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Cyanoacrylate Skin Microsealant for Preventing Surgical Site Infection after Vascular Surgery: A Discontinued Randomized Clinical Trial

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Abstract

Background: Surgical site infections (SSI) after vascular surgery are related to substantial morbidity. Restriction of bacterial access to the site of surgery with a cyanoacrylate sealant is a new concept. We performed a randomized clinical trial to assess the effect of the sealing of skin with a cyanoacrylate preparation at the site of surgery on the incidence of SSI after arterial reconstruction.

Methods: Patients scheduled for vascular reconstruction in or distal to the groin were randomized into a treatment and a control group. Standard measures for preventing contamination of the surgical field were taken in the control group, whereas cyanoacrylate was used as a skin sealant at the surgical site in the patients in the treatment group. We hypothesized that the incidence of SSI with the use of cyanoacrylate would be two-thirds (67%) lower than that with standard preparation of the surgical site, and performed an interim analysis of 50 patients to assess this.

Results: Risk factors among the 50 patients in the study included smoking (28%), hypertension (77%), diabetes mellitus (36%), and hypercholesterolemia (74%). Indications for surgery were invalidating claudication (Fontaine IIb), pain at rest, or tissue necrosis. The overall incidence of SSI was 3/47 (6%), without differences between groups; 9% SSIs in the control group versus 4% SSIs in the intervention group.

Conclusion: We could not confirm a reduction in the incidence of SSI after inguinal vascular surgery with the use of a cyanoacrylate skin sealant as compared with conventional means for preparing the surgical site.

The incidence of surgical site infection (SSI) shows wide variation, depending on patient-, surgeon-, and hospital-related factors. In inguinal vascular procedures, incidences of SSI of 7%–44% have been described [1,2]. Although surgical techniques have evolved considerably in recent decades, the incidence of SSI after vascular surgery, and its consequences, have not changed. In this context, groin infection in relation to the infection of prosthetic grafts in vascular surgery [3,4] is responsible for a high rate of limb loss and death [5].

Possible reasons for the relatively high incidence of infections in the groin in relation to the use of prosthetic vascular grafting to the femoral artery include the close proximity of the groin to the perineum, the relatively superficial position of these grafts, and the presence of lymphatic tissue ventral to the common femoral artery [6]. More than 50% of all SSIs are caused by endogenous bacteria [7]. The elimination of these micro-organisms could reduce the risk of groin infection after vascular surgery. A recent review and cost analysis found that replacement of iodine antisepsis by antisepsis with chlorhexidine was associated with statistically significantly fewer SSI (adjusted risk ratio 0.64, 95% confidence interval [CI] 0.51–0.80) [8]. However, the use of iodine draping did not significantly decrease the incidence of SSIs (risk ratio 1.03, 95% CI 0.064–1.66) [9].

Cyanoacrylate sealant is a film-forming liquid provided in a ready-to-use applicator that has been developed to bond to the skin surface. Cyanoacrylate was cleared in September 2006 (by the European Medicines Agency, London, United Kingdom) as a surgical drape accessory; it bonds to the skin

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upon application and immobilizes the bacteria that survive the application of antimicrobial products for surgical preparation of the patient's skin. The cyanoacrylate remains on the skin after completion of the surgical procedure and may prevent contamination of the surgical incision during the first few days post-operatively. Dohmen et al. studied the effect of cyanoacrylate on the incidence of SSI after coronary artery bypass grafting (CABG) [10]. They found that superficial or deep sternal SSI developed in seven patients (7.8%) in a control group (n = 545) as compared with only one patient (1.1%) in a group (n = 131) whose surgical site was applied with cyanoacrylate (OR 7.5, p = 0.062). Iyer et al. recently reported a significant reduction of SSI in the harvesting of portions of the greater saphenous vein when using a cyanoacrylate-based microbial sealant [11]. Only one SSI occurred (2.1%) in the group treated with sealant, whereas the incidence of SSI in the control group was 25.5% (n = 12, p = 0.001).

In the present study we tested the hypothesis that the additional attention given to the specific issue of SSI in a clinical study of its occurrence and the use of a cyanoacrylate skin sealant at the site of surgery could more than halve the incidence of SSI in the groin after vascular procedures, as compared with standard preventive measures. The study and the present report were done according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) Statement [12] .

Patients and Methods

Study design

We conducted a randomized, single-blind, clinical trial to evaluate the effect of a cyanoacrylate sealant on the incidence of groin infections after vascular surgery on the femoral artery. In the treatment arm of the trial, a ready-to-use applicator (IntéguSeal IS200, Kimberly-Clark, Roswell, GA) was used to apply the sealant to the incision site. Wounds were evaluated with the Southampton Wound Assessment (SWA) score [13]. In case of fluid evacuation from the wound bacterial cultures were taken.

During a pre-operative outpatient clinical visit, all consecutive adults over 18 y of age who had an indication for infrainguinal vascular reconstruction were informed about the study, and written informed consent was obtained from those who agreed to participate. The surgical procedures done on the patients in the study included femoro-popliteal, femoro-crural, and femoro-femoral crossover bypass graft implantation; excluded were thrombectomies done through an inguinal incision, patients younger than 18 y of age, and those with a previous groin incision or vascular reconstruction done cranially to the site of incision in the present study (e.g., endovascular aneurysm repair procedures). After signing an informed consent agreement, patients were randomly assigned in a 1:1 ratio to one of the two groups, with randomization accomplished by the drawing of a sealed envelope in the operating room one-half hour before surgery by the surgeon performing the operation. Ethical approval for the study was granted by the Committee on Research involving Human Subjects, Arnhem-Nijmegen, The Netherlands (reference NL25592.091.08).

Procedure

All patients received cepfazolin (Kefzol, Lilly, Houten, The Netherlands) 2 g IV prophylactically from 15–60 min before the incision for surgery was made. Patients were prepared in the routine manner for surgery, involving removal of hair with a clipper immediately before the procedure, disinfection with chlorhexidine 0.5% in 70% isopropyl alcohol, and sterile draping with disposable drapes (Secu-Drape, Sengewald, Germany). In the treatment group cyanoacrylate was applied to the site of surgical incision after regular disinfection but before incision, by pressing the foam tip of the applicator gently against the skin (Fig. 1). All patients underwent a wound evaluation at 2 d, 14 d, and 6 wk after operation. The wound evaluation was done at 2 wk and 6 wk post-operatively by a researcher who was blinded to the randomization done in the study, using the Southampton Wound Assessment (SWA) score [13] and maximizing correct definition through the additional use of wound culture results. A blinded wound evaluation at 2 d post-operatively was not possible. If a patient presented with a wound infection before the next scheduled wound evaluation, the infection was registered under the most recent previous evaluation. An efficacy interim analysis of the data was planned after inclusion of the first 50 patients.

Outcome measures

The primary endpoint of the study was the incidence of SSI within the first two post-operative weeks, defined as a SWA

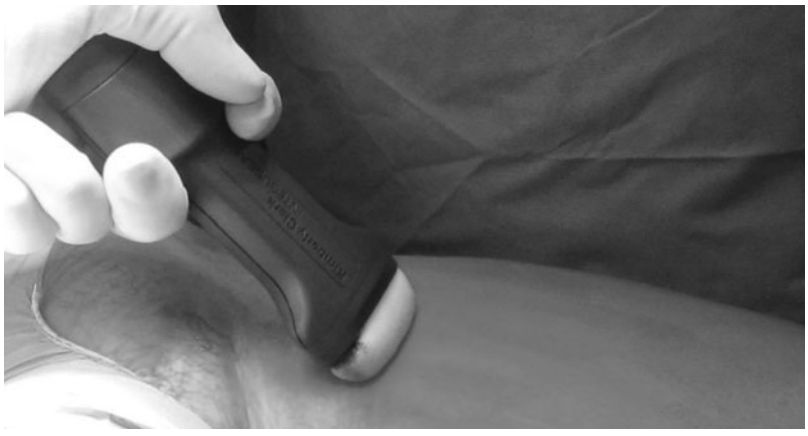

FIG. 1. The ready-to-use applicator for cyanoacrylate sealant in the groin of a patient.

Table 1. Southampton Wound Assessment Scale

	Clinical description
Grade 0	Normal wound healing
Grade I	Wound healing with mild bruising or erythema
A	Some bruising
B	Considerable bruising
C	Mild erythema
Grade II	Erythema plus other signs of inflammation
A	At one point
B	Around sutures
C	Along the wound
D	Around the wound
Grade III	Clear or serosanguinous discharge
A	At one point only (<2 cm)
B	Along the wound (>2 cm)
C	Large volume
D	Prolonged (>3 d)
Grade IV	Pus
A	At one point only (<2 cm)
B	Along the wound (>2 cm)

score of grade III or higher, in combination with a positive result of culture of a fluid specimen obtained aseptically from a primarily closed surgical site [14]. Criteria for SWA scores are given in Table 1 [13].

Sample size calculation

The mean incidence of vascular SSI as reported in the literature is 12% [1,2,6,13,14]. The assumption had been made that the use of a cyanoacrylate sealant would reduce the incidence of SSI by two-thirds of this reported value, from 12% to 4% [10,11], as compared with standard preventive measures. For trial demonstrating a superiority of cyanoacrylate with an effect size of 90% and a margin of 10%, 180 patients per group were needed (alpha 5%, power 80%) to provide a significant difference, as calculated in a power analysis. We performed a power analysis with the following formula [16]: $n = 8 \times (P_1[1-P_1] + P_2[1-P_2])/(P_1 - P_2)^2$, on the basis of an intention-to-treat principle. Significance was tested with the Fisher exact test. A value of $p < 0.05$ was considered significant.

Results

The study included 50 patients and was conducted from January 2010 to April 2011 at the Wilhelmina Hospital, Assen, The Netherlands. All patients approved their participation in the study. Three patients were excluded from analysis of the study data because of early post-operative death. Two of these three patients died from cardiac complications in the immediate post-operative period and the third died from bowel ischemia one week after vascular reconstruction in the groin (Fig. 2). As a result, a total of 47 groin incisions were available for analyses. Patients included in the analyses had a mean age of 71 ± 10 y, and 28 of the patients were male (60%). Co-morbidities included a history of smoking in 28% (13) of the patients, hypertension in 74% (36), diabetes mellitus in 36% (17), and hypercholesterolemia in 72% (34). In 68% (32) of the patients only a vascular reconstruction of the common femoral artery and its branches was performed. The remaining operations included 10 femoro-popliteal bypass procedures, one femoro-tibial bypass, two femoro-femoral cross-overs, and two endarteriectomies of the common femoral artery in combination with a percutaneous transluminal angioplasty (PTA) of the superficial femoral artery. The group in which cyanoacrylate was used and the group given standard

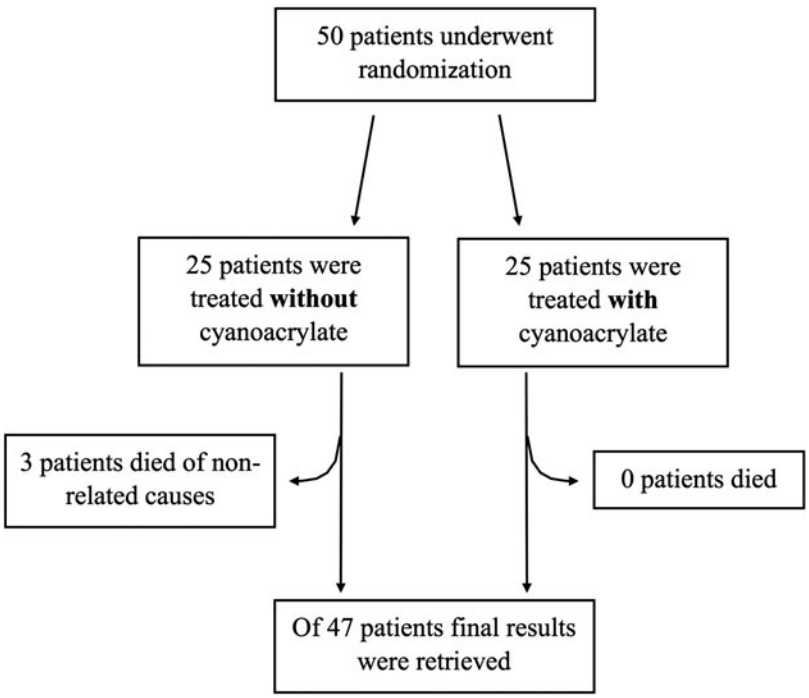

FIG. 2. Details of the screening and randomization procedures used in the study.

Table 2. Procedures and Risk Factors in Study Groups

	Group 1 (n = 22) Without CA	*Group 2 (n = 25) With CA*
Gender (male)	14 (64%)	14 (56%)
Smoking	7 (32%)	6 (24%)
Hypertension	19 (86%)	17 (68%)
Dyslipidemia	17 (77%)	17 (68%)
Diabetes mellitus	9 (41%)	8 (32%)
BMI (SD)	27 (4.6)	28 (4.5)
Age		
≤ 50 y	1 (5%)	1 (4%)
51–60 y	2 (9%)	5 (2%)
61–70 y	7 (32%)	9 (36%)
71–80 y	7 (32%)	4 (16%)
> 80 y	5 (23%)	6 (24%)
Fontaine IIa	4	2
Fontaine IIb	9	12
Fontaine III	6	8
Fontaine IV	3	3
Common femoral reconstr.	16 (73%)	16 (64%)
Femoro-popliteal bypass	3 (14%)	7 (28%)
Femoro-crural bypass	1 (5%)	0
Crossover bypass	0	2 (8%)
Other	2 (9%)	0
Mean operating time, min (SD)	132 (41.4)	151 (48.0)

BMI = body mass index; CA = cyanoacrylate.

surgical preparation were comparable with regard to the types of procedures and risk factors in each group (Table 2).

The overall incidence of SSI was 6% (3 patients) (Table 3). At all measured time points, the difference in incidence of SSI in the treatment and control groups was smaller than expected (in the control group, two infections were diagnosed, on post-operative days 6 and 18, respectively, and in the treatment group, one infection was diagnosed, on post-operative day 22) (Fig. 3). The two infections in the control group were caused

Table 3. Number of SSIs in Study Groups

	No SSI	*SSI*
Cyanoacrylate (−)	20 (91%)	2 (9%)
Cyanoacrylate (+)	24 (96%)	1 (4%)

SSI = surgical site infection.

by *Staphlyococcus aureus* and *Pseudomonas aeruginosa*. The patient with SSI in the group treated with cyanoacrylate, took a bit longer to develop symptoms and had only *S. aureus* in its culture.

The two patients in the control group who developed infections underwent endarterectomy of the common femoral artery, with venous patching. They were treated empirically with oral antibiotics (amoxicillin/clavulanic acid 625 mg for 3 d), and their wounds were opened and rinsed with sterile water twice a day until closure. Both healed without further complications. A re-operation at 22 days after initial surgery was required in the patient in the cyanoacrylate group who developed a SSI because of an infected polytetrafluoroethylene femoro-femoral crossover bypass.

Lymphatic complications occurred in two patients each, in the cyanoacrylate and control groups. All of these patients had sterile fluid draining from their surgical incisions, as confirmed by negative cultures in all four cases.

Discussion

An interim analysis of the data in the present study suggested that the use of cyanoacrylate does not reduce the incidence of SSI after inguinal vascular surgery. However, the overall incidence of SSI was 6%, which was one-half the expected incidence in the control group. Re-calculations based on a 6% incidence in the control and 3% incidence in the cyanoacrylate treatment group showed that 748 patients would have been required in each study group to reach an adequate statistical power. However, even with this number

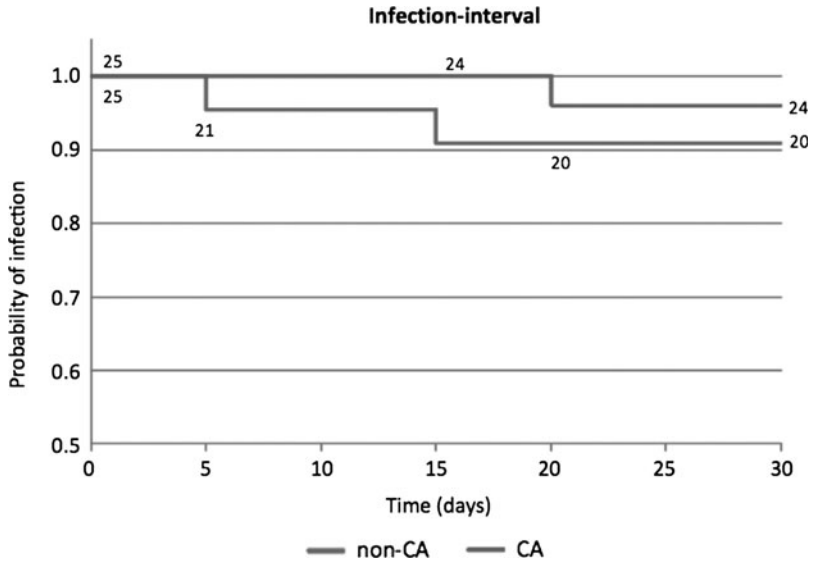

FIG. 3. Kaplan–Meier curve of 25 patients treated with cyanoacrylate skin sealant before surgery (treatment group) and 25 patients prepared for surgery without cyanoacrylate (control group).

of patients no superiority might be demonstrated from the use of cyanoacrylate in preventing SSI if the current findings are representative. The review board that provided ethical approval for the study deemed the number of patients that would have been required for adequate statistical power to be too large for the purpose of the study, and the study was therefore stopped.

The assessment of risk for SSIs in the groin is complex. Besides being affected by age, obesity, duration of operation, duration of hospital stay, and co-morbid conditions such as diabetes mellitus and ASA status [17], the incidence of such infections is also affected by the indication for surgery, with patients who have critical limb ischemia (CLI) having a higher incidence of SSI [4]. Exposure of the femoral artery in the Scarpa triangle results in transection of lymphatic vessels [18], possibly increasing the risk of infection. Results are conflicting for the effect of the type of incision made for exposure of the femoral artery on the incidence of SSI [6,15]. The use of adhesive drapes does not seem to influence the incidence of SSI. A review including five studies involving 3,082 participants in which adhesive drapes were compared with the non-use of drapes, and two studies involving 1,113 participants in which iodine-impregnated adhesive drapes were compared with the non-use of drapes, concluded that there is no evidence that plastic adhesive drapes reduces the incidence of SSI. Contrastingly, there is even evidence that they may increase rates of infection, and it was for this reason that the control group in the present study was given only standard measures for preventing infection [9].

In previous studies, the use of cyanoacrylate to seal bacteria to the skin of patients undergoing surgery reduced significantly the incidence of SSI [10,11]. This contrasts with the results of the present study. Various factors may explain the difference. First, the study conducted by Dohmen et al. had a selection bias [10]. Patients treated with the cyanoacrylate sealant in their study underwent surgery by one surgeon, whereas patients in the control group were treated by other surgeons. Second, the operations done both by Iyer et al. and done by Dohmen et al. [10,11] were performed in clean areas of the body, whereas the groin is usually considered to be clean-contaminated. A higher overall incidence of SSI could therefore have been expected. The skin of the groin is known to contain more sweat glands, and develops folds in a seated patient, thereby creating an environment for microbial contamination [18]. Moreover, these folds increase the flexibility of the skin in the groin, thereby causing multiple cracks to develop in the sealant and counteracting its mechanism of action. A recent trial confirmed our conclusion in showing no significant decline in the incidence of SSI in 496 incisions treated with the same cyanoacrylate sealant as used in our study [19]. A better surgical site for research on the use of cyanoacrylate would be the area of the carotid artery, but because SSI in this area is rare, larger study groups would be needed to provide statistical power in a comparison of cyanoacrylate with other preparative techniques for carotid surgery.

The present study has several limitations. First, the study was a randomized, single-site trial, and may therefore have been susceptible to patient selection. Second, the preponderance in the study of non-smokers and patients without CLI was surprisingly high (72% and 87%, respectively), which may well have affected the incidence of SSIs. Unfortunately, screening for colonization with *S. aureus* was not performed pre-operatively. All cultures of the infected infections contained *S. aureus*, and they could possibly have been prevented had preoperative eradication been performed [20]. Additionally, most of the surgical procedures done in the study consisted solely of a reconstruction of the common femoral artery, and the performing surgeon was informed about the allocation of the patient, thereby creating the risk of bias in the conduct of the surgeon. All of the foregoing factors may have attributed to the relatively low incidence of infections in the present study.

In conclusion, we could not show a reduction in the incidence of SSI in the groin after vascular surgery following the use of a cyanoacrylate skin sealant. The number of patients needed to treat to reach statistical significance was considered too great for clinical relevance of the findings in the present study. A multi-center trial, preferably including older patients with CLI, may show significance with a lower number-needed-to-treat of patients for such a finding.

Author Disclosure Statement

The authors declare they have no conflicts of interest and received no funding.

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