Chirurgia (2022) 117: 651-659
No. 6, November - December

http://dx.doi.org/10.21614/chirurgia.2794

Prediction and Management of Surgical Site Infections in Hybrid Vascular Surgery for Peripheral Artery Disease

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Received: 26.10.2022
Accepted: 12.12.2022

Rezumat

Predicția și managementul infecțiilor de situs operator în intervențiile vasculare hibride pentru boala arterială periferică

Obiective: O problemă importantă cu care se confruntă toți chirurgii este reprezentată de complicațiile postoperatorii. Dintre acestea, infecțiile locale şi sistemice sunt printre cele mai răspândite evenimente adverse post-procedurale. Pentru realizarea acestui studiu am urmărit anumite investigații de bază care ne pot sugera probabilitatea unui astfel de eveniment precum si anumite semne evaluabile clinic. Examinarea detaliată a pacientului este crucială pentru predicția şi prevenția infecțiilor de situs operator (ISO) şi fiecare informație suplimentară ne poate ajuta sa reducem incidența acestor complicații postoperatorii.
Metode: Am realizat un studiu observațional multicentric, retrospectiv şi prospectiv în perioada 01.01.2019 – 01.09.2021. Pacienții incluşi în studiu au fost adulți diagnosticați cu boală arterială periferică (BAP) cu claudicații intermitente invalidante sau durere de repaus. Am exclus minorii şi urgențele chirurgicale (anevrisme rupte, ischemii acute sau traumatisme vasculare). Am urmărit complicațiile postoperatorii, precum şi managementul acestora, si am pus accent pe infecțiile de situs operator. Pentru a determina valorile cheie de relevanță statistică am utilizat curbe de probabilitate ROC (Receiver Operating Characteristic) cu măsurarea AUC (Area Under the Curve). Am utilizat analiză multivariată pentru a evalua relevanța statistică a datelor noastre.
Rezultate: Studiul evaluează 128 de pacienți diagnosticați cu BAP,

cu vârste cuprinse între 47 şi 97 de ani, cu o medie de vârstă de 71,26 ± 10,8 ani. Au fost semnificativ mai mulți pacienți de sex masculin, 71,09% (p < 0,01). Toți pacienții au fost tratați folosind tehnici vasculare hibride (chirurgie convențională combinată cu tehnici endovasculare). Toate complicațiile au fost consemnate, dar ne-am concentrat pe ISO, fiind cea mai prevalentă complicație (25%). Au fost urmăriti factorii care au influențat aparitia infectiilor locale de situs operator. O valoare preoperatorie mai mare de 5 mg/dl a Proteinei C-Reactive (CRP), a fost confirmată ca şi factor predictiv pozitiv pentru ISO (AUC = 0,80). Un alt factor predictiv pozitiv, confirmat pentru ISO, a fost hiperglicemia; valorile glicemice preoperatorii mai mari decât 140mg/dl au fost associate cu infecțiile postoperatorii (AUC = 0,71). ISO au avut o incidență crescută la pacienții cu leziuni trofice distale preoperatorii (p < 0,01). Prezența altor complicații, cum ar fi edemul şi limfocelul, au crescut de asemenea incidenta infectiilor de situs operator (p < 0,01). Cu toate acestea, pacienții pentru care s-a realizat tratamentul chirurgical al plagii infectate precum si pacientii care au beneficiat de terapie cu presiune negativă a plăgii (NWPT) au avut spitalizări semnificativ mai scurte decat pacienții tratați doar medical (p < 0,01).
Concluzii: Există multipli factori clinici şi paraclinici cu caracter predictiv pozitiv pentru ISO. Coexistența mai multor astfel de factori poate asocia un risc suplimentar de dezvoltare a ISO şi fiecare dintre aceştia ar trebui evaluat şi controlat separat în faza preoperatorie. Admiterea într-un centru de diabetologie şi reglarea valorilor glicemice înainte de operațiile vasculare elective, pentru pacienții care pot fi amânați chirurgical este o metodă eficientă de prevenire a infecțiilor. Managementul chirurgical rămâne cea mai eficientă metodă de tratament al ISO, oferind rezultate imediate şi reducând timpul de spitalizare.

Cuvinte cheie: chirurgie vasculară hibridă, BAP, infecții de situs operator, CRP, hiperglicemie

Abstract
Objectives: Postoperative complications are an important problem that all surgeons face. Among all possible complications, local and systemic infections are one of the most prevalent post-procedural adverse events. It is difficult to assess whether or not a patient will develop a surgical site infection (SSI), but there are certain basic investigations that can suggest the probability of such an event. We also investigated some clinically assessable signs to help us better predict the occurrence of SSIs. Every bit of information brings us closer to an ideal where we can bring postoperative complications to a minimum. Close examination and attention to detail is crucial in the prediction and prevention of SSIs.
Methods: A multicenter, retrospective and prospective observational study was carried out between 01.01.2019 – 01.09.2021. All adult patients with peripheral artery disease (PAD) who had disabling intermittent claudication or rest pain, were included in this study. We excluded minor or vascular surgery emergencies (ruptured aneurysms, acute ischemia or vascular trauma). We followed the postoperative complications as well as their management with an emphasis on surgical site infections (SSIs). Receiver Operating Characteristic (ROC) curves were used to determine key values of statistical relevance by calculating the Area Under the Curve (AUC). Multivariate analysis was used to assess the statistical relevance of our data.
Results: The study evaluates 128 patients diagnosed with PAD, aged between 47 and 97, with a mean age of 71.26 ± 10.8 years. There were significantly more male than female patients 71.09% vs. 28.91% (p < 0.01). All patients were treated using hybrid vascular techniques. All complication rates were recorded but we focused on SSIs, which was the most prevalent complication (25%). C-Reactive Protein with values higher than 5 mg/dl, was confirmed as a positive predictive factor for postoperative surgical site infections (AUC = 0.80). Another positive predictive factor for SSIs is hyperglycemia. Glycemic values higher than 140mg/dl are more frequently associated with postoperative infections (p = 0.02), a predictability curve of

statistical significance was also obtained (AUC = 0.71). Postoperative SSIs were more prevalent in patients with preoperative distal trophic lesions ($p < 0.01$). The presence of other complications such as edema and lymphoceles were also linked to SSIs ($p < 0.01$). Nevertheless, patients who underwent surgery over negative wound pressure therapy (NWPT) for infection management had significantly shorter hospital stays ($p < 0.01$).
Conclusions: There are multiple clinical or paraclinical predictors of SSIs. The coexistence of several such factors can carry an additional risk of developing a SSI and should be evaluated and controlled separately in the preoperative phase as much as possible. Admission to a diabetes center and regulation of glycemic values prior to elective vascular surgery, for patients who can be surgically postponed is an effective method of preventing infections. Surgical management remains the most reliable form of treatment of SSIs, being the most efficient therapy and offering immediate results, while simultaneously shortening hospital stays.

Key words: hybrid vascular surgery, PAD, SSI, CRP, hyperglycemia

Introduction

Postoperative complications are an important problem that all surgeons face. Among all possible complications, local and systemic infections are one of the most prevalent post-procedural adverse events. The incidence of infectious complications for lower limb surgical revascularization procedures in high-risk patients can reach up to 30% (1-5). This increases the mortality rate and lengthens hospital stay as well as increasing hospital expenses (6,7). Surgical site infections were also associated with an increased rate of reintervention and major amputation (8). There are multiple assumptions related to which factors influence the occurrence of post-operative infections. These could be related to the patient's pathology and associated morbidities as well as extrinsic parameters such as hospital type and size (teaching hospitals where residents learn to operate have significantly more postoperative infections), procedure length and the solutions used to prepare operative sites (8-10).

It is difficult to estimate whether or not a patient will develop a surgical site infection, but there are certain basic investigations that can suggest the probability of such an event. Among these are C-reactive protein (CRP) and glycemia. CRP is a protein secreted in the liver, as an inflammatory response to the action of cytokines, which has a relatively short life span (19 hours half-life) and can be monitored proactively (11). It binds to certain molecular structures that are generally found on the surface of pathogenic bacteria and on certain cellular fragments of dead cells (12). Poor glycemic control is also responsible for infections by lowering the effectiveness of the immune system due to a series of cellular metabolic alterations. High blood sugar levels inhibit the production of oxygen radicals by neutrophils, the release of interleukin 1 (IL-1) by macrophages, and also hinder the process of phagocytosis (13). The weakened immune system does not respond adequately when stimulated and paves the way for surgical site infections.

In addition to previously described factors, it is possible to try and control the pathogens responsible for SSIs through appropriate antibiotic therapy. Even though, in theory, there is a very large number of pathogens that can cause the infection of a surgical wound, in our daily clinical practice there are very few bacteria that are usually responsible for most infections. The most frequently encountered pathogens are Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas

aeruginosa (14-17). Considering this, an effective antibioprophylaxis can be achieved using broad-spectrum antibiotics, that are mainly effective on these pathogens, as well as covering a broad range of the spectrum. Antibiotic prophylaxis is a surgical standard in modern medical practice, thus all patients benefit from 24 hours of perioperative antibiotherapy, this being an effective method of reducing the incidence of local postoperative infections (18). Prolonged administration of antibiotics for all patients is not justified because there is no evidence favoring the effectiveness of long-term antibiotic treatment in preventing surgical site infections (19-21).

Every bit of information brings us closer to an ideal where we can bring postoperative complications to a minimum. Close examination and attention to detail is crucial in the prediction and prevention of SSIs.

Materials and Methods

A multicenter, retrospective and prospective observational study was carried out between 01.01.2019 – 01.09.2021. All adult patients with PAD who had disabling intermittent claudication or rest pain were included in this study. We did not include minor or vascular surgery emergencies (ruptured aneurysms, acute ischemia or vascular trauma).

For more accurate results, we investigated the following parameters: general data (age, weight, height, body mass index - BMI), clinical examination (claudication distance, rest pain, trophic lesions, peripheral pulses, disease classification), cardiovascular risk factors (diabetes, smoking, dyslipidemia, blood pressure), medical and surgical history, paraclinical investigations (ankle-brachial index - ABI, peripheral transcutaneous oxygenation - TcPO2, Doppler ultrasound, Computed Tomography Angiography - CTA, echocardio-graphy), laboratory tests, and preoperative medication. Certain parameters, such as ABI and TcPO2 were measured both preoperatively and postoperatively in order to objectively evaluate procedural effectiveness. For diabetic patients, Metformin was not administered for 48 hours, starting on the day of surgery. Anticoagulants and antiplatelet agents were discontinued preoperatively as follows: vitamin K antagonist (VKA) - 6 days (in cases of chronic limb threatening ischemia, 10 mg of vitamin K was administered and the International Normalized Ratio (INR) was monitored; this process could be repeated several times until a target value equal to or inferior to 1.5 was reached), Apixaban - 72 hours, Rivaroxaban - 72 hours, Fondaparinux - 36-42 hours, Clopidogrel - 7 days, Ticagrelor - 5 days, Aspirin was not discontinued preoperatively. For each hybrid intervention, we administered 50 U.I heparin/kg intraoperatively.

Antibiotic prophylaxis of postoperative infections was carried out for all our patients by short-term antibiotic administration (24 hours), or with prolonged administration for those with local or systemic infections diagnosed preoperatively.

We followed the postoperative complications as well as their management and we established links between the preoperative data and the incidence of local and systemic complications with an emphasis on surgical site infections. Receiver Operating Characteristic curves were used to determine key values of statistical relevance by calculating the Area Under the Curve. Multivariate analysis was used to assess the statistical relevance of our data. This study was approved by the research ethics committee of the University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania.

Results

The study evaluates 128 patients diagnosed with PAD, aged between 47 and 97, with a mean age of 71.26 ± 10.8 years. There were significantly more male than female patients 71.09% vs. 28.91% ($p < 0.01$). All patients were treated using hybrid vascular techniques. Risk factors and associated morbidities were recorded for all participating patients (*Table I*).

Following revascularization, we had a

Table 1. General information, risk factors, and associated morbidities

Variable	n (%)
General	
Sex, M	91 (71.09)
Sex, F	37 (28.91)
Reason for admission	
Invalidant claudication	52 (40.63)
CTLI*	76 (59.38)
Risk factors	
Smoking	94 (73.44)
Diabetes	51 (39.84)
Dyslipidemia	102 (79.69)
Morbidities	
Hypertension	102 (79.69)
CKD** (GFR*** < 30)	4 (3.13)
Coronary artery disease	38 (29.69)
Cerebrovascular disease	40 (31.25)
Heart failure	49 (38.28)
COPD****	19 (14.84)

CTLI* – Chronic Limb Threatening Ischemia
CKD** – Chronic Kidney Disease
GRF*** – Glomerular Filtration Rate
COPD**** – Chronic Obstructive Pulmonary Disease

Table 2. Postoperative complications

Postop complications	n (%)
Infection	32 (25.00)
Bleeding	12 (9.38)
Thrombosis	6 (4.69)
Lymphorrhagia	7 (5.47)
Lymphocele	16 (12.50)
Hypoesthesia	24 (18.75)
Paresthesia	15 (11.72)
Oedema	24 (18.75)
Reperfusion injury	10 (7.81)
Compartment syndrome	1(0.78)
False Aneurysm	1(0.78)
DVT*	1(0.78)
AKF**	1(0.78)
AMI***	2(1.56)
HIT****	2(1.56)
Death	1(0.78)
Other	3(2.34)

DVT* – Deep Vein Thrombosis
AKF** – Acute Kidney Failure
AMI*** – Acute Myocardial Infarction
HIT**** – Heparin Induced Thrombocytopenia

series of complications of varying complexity (*Table 2*) for which medical or surgical management was chosen, depending on their type and severity. SSIs were the most frequent postoperative complication encountered (25%). Infection management was achieved by antibiotherapy (100%), negative wound pressure therapy (18.75%), and by surgical means (59.38%). Patients who underwent surgery over negative wound pressure therapy for infection management had significantly shorter hospital stays ($p < 0.01$).

We confirmed that preoperative CRP is a positive predictive factor for SSIs. In our study, patients with preoperative high CRP values (> 5 mg/dl), were more likely to develop SSIs in the first week after surgery. This was achieved statistically by using a ROC curve (AUC = 0.80) (*Fig. 1*). Another investigation with similar results regarding its role in predicting SSIs was glycemia. We showed that hyperglycemia (> 140 mg/dl) is more frequently associated with postoperative infections ($p = 0.02$). We also obtained a predictability curve of statistical significance (AUC = 0.71) (*Fig. 2*). We noticed that patients who were previously admitted to a diabetes unit for proper preoperative glycemic control had a significantly lower SSI rate ($p < 0.01$).

On admission, 48.44% of patients had distal trophic lesions. Postoperative SSIs were more common in patients with preoperative trophic lesions ($p < 0.01$). However, this direct causal relationship was not confirmed for patients with trophic lesions who also under-

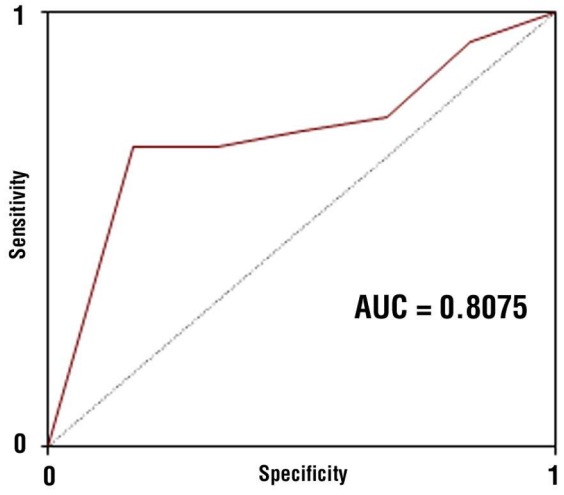

Figure 1. ROC curve for preoperative CRP

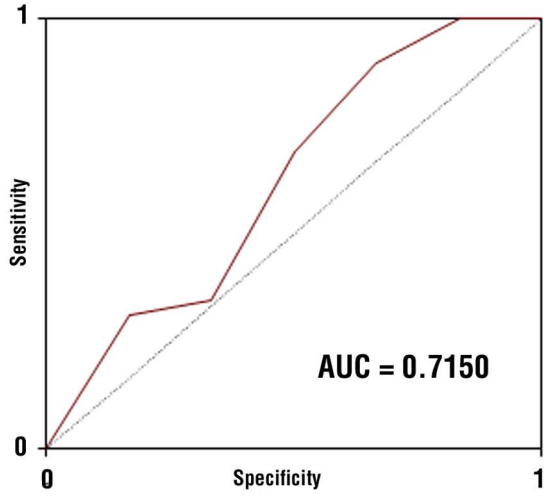

Figure 2. ROC curve for preoperative glycemia

went a minor amputation within the main procedure.

A percentage of 12.5% of patients developed lymphocele after revascularization, which was also surgically evacuated in most cases due to infection. This was yet another predictive factor as patients with lymphocele were more likely to develop SSIs. Out of 16 patients with lymphocele, 12 had a SSI ($p < 0.01$). Only for patients with moderate postoperative lymphorrhagia (5.47%) was lymphostasis attempted by using compressive bandages.

Postoperative edema was present in 18.75% of patients. We found that this complication occurs more frequently in patients with a preoperative peripheral transcutaneous oxygenation (TcPO2) lower than 39 mmHg ($p < 0.01$). Furthermore, out of 24 patients with edema, 18 developed SSIs ($p < 0.01$).

Patients' surgical history showed that 51.56% of all patients had at least one previous arterial revascularization procedure for PAD (endovascular or conventional surgery) and 20.31% of all patients had prior coronary revascularization (classic or interventional). In our case we did not find any relevant difference, in terms of infections, between patients with redo interventions and those with de-novo revascularizations ($p = 0.15$).

Discussions

C-reactive protein has been repeatedly shown to be an indicator and positive predictive factor of postoperative infections (22-24). It is also a predictor for long-term mortality and major cardiovascular events (25), as well as predicting the severity of peripheral vascular disease (26). In our study, CRP values higher than 5 mg/dl were associated with an increased prevalence of surgical site infections.

Another commonly investigated factor that has an important role in predicting postoperative infections is blood glucose (27-29). Inadequate perioperative glycemic control is also associated with an increased rate of postoperative mortality and morbidity in vascular patients (30). We confirmed this in our group of patients, for whom we associated preoperative glycemic values with the incidence of postoperative infectious complications and showed that SSIs are significantly more frequent in patients with poor glycemic control (glycemia > 140 mg/dl).

In certain cases, preoperative stabilization of paraclinical parameters or at least maintaining them in the optimal functioning range can be a real challenge, especially for patients with chronic limb threatening ischemia (CLTI) for whom postponing the revascularization procedure could lead to major amputation. Vascular patients for whom revascularization can be delayed, adequate glycemic control prior to surgery, preferably in a diabetes unit, could reduce surgical site infections rates. This has been demonstrated in the case of cardiac and digestive surgery interventions (31) and should be investigated in detail for patients with peripheral artery disease.

We also found that the presence of preoperative trophic lesions is associated with an increased incidence of postoperative infections ($p < 0.01$). Trophic lesions in patients with peripheral arterial disease can cause sepsis or even endocarditis in certain cases (32-34). These are severe events that increase the mortality rate of vascular patients. There is an ongoing study investigating the 30-day

mortality rate for patients with PAD and sepsis admitted to the medical intensive care unit (Peripheral Artery Disease and Sepsis Outcomes - NCT03372330). We also noted the fact that patients with associated trophic lesions, for whom a minor amputation was performed at the end of the revascularization procedure, had a lower SSI rate than patients with trophic lesions for whom such an amputation was not performed during the main intervention, this being achieved in the following days or weeks as a separate procedure. Although many patients are refractory to the idea of amputation, and might need more time to process the information, this could reduce the rate of postoperative infections, if it is performed during the main procedure, after the sterile dressings are applied to the vascular site incisions. Another benefit to this is the use of the same anesthesia to perform both the revascularization as well as the minor amputation, thus reducing the incidence of possible complications related to performing another anesthesia as well as reducing hospital expenses and average hospital stay. Of course, the latter is only a clinical observation, valid only for our patient group, and it requires additional research for scientific validation.

Lymphocele is a relatively frequent postoperative complication in vascular surgery and generally affects groin incisions. It is responsible for surgical reinterventions and other local infectious complications (35). Our patients who developed lymphocele postoperatively were much more likely to develop an operative site infection (out of 16 patients with lymphocele, 12 developed local infection; $p < 0.01$). Careful follow-up of patients and local wound inspection could avoid early readmissions or severe infections with delayed treatment, which would increase morbidity and mortality rates.

We have described several factors with a positive predictive role for speculating postoperative infections, namely: C-reactive protein higher than 5 mg/dl, glycemic levels higher than 140mg/dl and the presence of preoperative distal trophic lesions. We named the coexistence of these factors, the CGL triad (C reactive protein – Glycemia – trophic Lesions). CGL can be positive, when all three components are present, or negative, when at least one of its elements is missing. Among the patients with a positive preoperative CGL, we found that 50.25% developed a SSI in the first week. Of course, this fact must be thoroughly investigated and extrapolated to all patients with peripheral arterial disease.

Postoperative edema is a frequently encountered complication for lower limb revascularization candidates. It has a high incidence and can be present in up to 100% of cases, especially in patients in whom a by-pass is performed using an autologous internal saphenous vein graft. Edema is generally present postoperatively for patients with infrainguinal lesions and is less often encountered in aorto-iliac revascularizations (36-38).

Our complication rates do not differ significantly from the data found in international databases, falling within the stipulated percentages. Of course, there is a slight variation, which depends on the operating team as well as the experience of all the medical and paramedical personnel who cares for the vascular patients. This might be responsible for the small differences between the studies carried out by the medical scientific community. Strict protocols and postoperative nursing guidelines, combined with the experience of a specialized medical staff could further reduce the risk of adverse events.

In the framework of hybrid interventions, we share more of the postoperative complication rates of conventional surgery rather than those of endovascular procedures, a fact that is otherwise obvious since we are talking about the complications related to a surgical incision under general anesthesia compared to a percutaneous puncture under local anesthesia.

Regarding the management of SSIs, targeted antibiotic therapy is the standard therapy used in all patients regardless of what other techniques are applied. Most patients require surgical treatment which is currently the safest and the best way to remedy infectious complications with immediate results (39,40).

For local infections that do not affect the entire wound or in cases where a synthetic graft was not used negative wound pressure therapy can also be opted for. NWPT is superior to the basic adhesive dressings, reducing the spread of the infection and favoring controlled healing (41).

Conclusions

There are multiple clinical or paraclinical predictors of SSIs. The coexistence of several such factors can carry an additional risk of developing a SSI and should be evaluated and controlled separately in the preoperative phase as much as possible.

Admission to a diabetes center and regulation of glycemic values prior to elective vascular surgery for patients who can be surgically postponed is an effective method of preventing infections.

Surgical management remains the most reliable form of treatment of SSIs, being the most efficient therapy and offering immediate results, while simultaneously shortening hospital stays.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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