University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medicine

The Clinical Impact of Access Site Selection for Successful Lower Limb Interventions

Summary of PhD Thesis

Adam Janos Csavajda, MD

Supervisor: Zoltan Ruzsa, MD, PhD

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1. INTRODUCTION

Peripheral arterial disease (PAD) is an extremely common and complex condition, affecting nearly 200 million people worldwide. Its clinical manifestations are critical limb ischemia (CLI) and acute limb ischemia (ALI). These conditions are of great clinical importance due to the severe complications they can cause, as well as there high rates of comorbidity and mortality. Symptoms may present as pain at rest or, in more severe cases, as tissue damage in the form of ulcers and/or gangrene. The prevalence of PAD in patients with serious comorbidities and complex anatomy is steadily increasing, which has led to the rapid development and broader application of endovascular interventions.

Recent advances in endovascular therapy have enabled prompt treatment of PAD; however, most procedures are still performed via traditional femoral access sites. The femoral artery (FA) puncture remains a universally accepted entry point for lower extremity interventions, and it has stood the test of time. It is still widely used for several reasons: it is easy to access, it allows for the use of larger devices due to the vessel's larger caliber, and the complications associated with the puncture, along with their treatment options, are well understood. Despite these advantages, the femoral access site has several disadvantages that are not encountered with other access points, such as prolonged bed rest and a higher incidence of vascular complications. However, it is important to note that the safety of the femoral approach has significantly improved

with the widespread adoption of ultrasound-guided puncture and vascular closure devices.

Alternative access sites in PAD treatment include the upper limb arteries - the radial (RA) and brachial arteries (BA) – as well as pedal access. However, these sites have several limitations in everyday clinical practice. Despite these technical limitations, they have gained significant popularity in the field of peripheral interventions because they offer greater patient comfort and are associated with fewer vascular access site complications. This trend aligns with the current direction in healthcare to provide safe, effective care while reducing costs and minimizing risks.

2. OBJECTIVES

The aim of this doctoral thesis is to analyze the access sites used during peripheral interventions in terms of the anatomical approach, indications, advantages, disadvantages, and potential complications. Additionally, it presents the current state of peripheral interventional vascular approaches through three different clinical trials and interprets the scientific contribution of these results in the field of peripheral interventions.

2.1 Research 1 - The Clinical Impact of Access Site Selection for Successful Thrombolysis and Intervention in Acute Critical Lower Limb Ischaemia (RAD-ALI Registry)

ALI is of great clinical importance due to its consequent serious complications and high comorbidity and mortality rates. Current advances in endovascular therapy enable prompt treatment of

ALI; however, most treatment is performed via traditional FA access sites. Alternatives to FA access in ALI are the upper limb access sites of the RA and BA or pedal access, but these access sites have many limitations in everyday clinical practice. Our primary aim was to investigate the rate of complications related to the access site in patients with acute limb vascular occlusion. In addition to the objective that forms the basis of this thesis, our additional goal was to investigate the 1-year outcomes of catheter directed thrombolysis (CDT) and mechanical thrombectomy (MT) for ALI and to evaluate predictors of long-term outcomes of CDT and MT in lower limb arteries.

2.2 Research 2 - TRIACCESS Study: Randomized Comparison Between Radial, Femoral, and Pedal Access for Percutaneous Femoro-popliteal Artery Angioplasty

The main anatomical limitation of percutaneous superficial femoral artery (SFA) interventions is the narrow access lumen in the case of upper extremity and below-the-knee (BTK) arteries, while in the case of RA the limitation is the distance between the puncture point and the target lesion. The aim of this randomized study was to compare the success and complication rates of different access sites during the percutaneous endovascular treatment of SFA stenoses, as well as the crossover to another puncture site.

2.3 Research 3 - Distal Radial Artery Access for Superficial Femoral Artery Interventions

The standard access site used during coronary interventions is the PR artery, which has recently gained more popularity in peripheral interventions as well, due to better patient comfort and the low rate of major access site complications. During percutaneous SFA interventions, the PR access has a high technical success rate and a low rate of major access site complications, but radial artery occlusion (RAO) occurs in up to 5%. DR artery access, initially only used during Cimino fistula percutaneous transluminal angioplasties (PTAs), is now used during both coronary and peripheral interventions. The main advantages of this type of access are easy compressibility and a low incidence of RAO. The aim of this study was to evaluate the acute success and complication rates of DR approach and to compare it with the results of conventional PR approach during SFA interventions.

3. METHODS

3.1 Research 1 - Study Design and Patient Population

Between 2008 and 2019, consecutive patients with ALI were treated with CDT in a large community hospital. We collected the data of these patients and performed a retrospective analysis. We enrolled only patients who, based on the decision of the vascular team, underwent CDT. Patients were randomized to the RA (n=17), BA (n=9) and FA (n=58) groups. Access site selection was operator decision and all procedures were performed by five skilled operators. The National Ethical Review Committee (reference number BMEÜ/1639-1/2022/EKU) approved the study. All study activities were in accordance with the ethical standards of the Hungarian

Medical Research Council and with the 1964 Helsinki Declaration. Written informed consent was obtained from all patients prior to their inclusion in the study. We performed a retrospective, single center trial (Bacs-Kiskun County Teaching Hospital, Kecskemet, Hungary).

Inclusion criteria included patients with ALI classified as Rutherford stage I, IIA, or IIB, acute lower extremity vascular occlusion confirmed based on emergency diagnostic angiography, clinic attendance starting within 14 days, age>18 years, and they had signed the patient information sheet and consent form. Patients were excluded if they had a non-viable lower limb (Rutherford stage III), did not sign the patient information sheet or the consent form, had hemodynamic instability, did not have significant vascular occlusion on diagnostic angiography, were not admitted to the clinic within 14 days; age<18 years, had inflammatory skin lesions at the planned penetration sites, and presence of contraindications for acute lower extremity thrombolytic therapy.

Primary endpoints ("safety endpoints") were major adverse events (MAEs), major adverse limb events (MALEs), and occurrences of complications related to the access site. Secondary endpoints ("efficacy endpoints") were technical and clinical success, efficacy of the treatment, fluoroscopy time, radiation dose, procedure time, and the crossover rate to an alternative puncture site.

3.2 Research 2 - Study Design and Patient Population

In the prospective, multicenter study conducted between 2018 and 2019, 180 symptomatic patients with SFA stenosis were randomized between RA (n=60), FA (n=60) and TP (n=60) access

site groups. Randomization was performed blindly using sealed envelopes. All cases were performed by 3 operators trained in both transradial and transpedal access sites. The National Ethical Review Committee (OGYÉI/2499/2018) approved the study, and all patients signed a patient informed consent form before enrollment.

Inclusion criteria included patients with significant SFA stenosis, claudication (Fontaine IIa, IIb, III, IV), or CLI (ischemic rest pain, crural or pedal ulcer, and gangrene). Patients were excluded who did not have access to all the penetration gates (RA, FA, TP) recorded in the study, occlusion of more than 2 BTKs, isolated popliteal artery disease, non-viable lower limb, strict contraindication to double antiplatelet therapy planned for at least 1 month, heart failure (ejection fraction<35%), significant valvular disease, age over 85 years, severe renal failure (glomerular filtration rate<30 mL/kg), sepsis, a co-morbidity with a life expectancy of less than 3 years.

Primary endpoints were major adverse limb and cardiac events at one- and six-month follow-up periods, procedural success. Secondary endpoints were clinical success, occurrence of complications related to the access site, procedural or renal complications, hospitalization time, fluoroscopy time, radiation dose, procedure time, contrast consumption and the crossover rate to an alternative puncture site.

3.3 Research 3 - Study Design and Patient Population

Between 2016 and 2019, 195 patients with symptomatic SFA stenosis (>70% diameter stenosis) underwent PTA through RA penetration using sheathless guiding. We intervened on 38 patients

with DR access (mean age 68.5 ± 8.5 years; 26 men), and 157 patients (mean age 67.3 ± 9.8 years; 101 men) with PR access. Patients in whom we could not reach the CFA with the 125 cm diagnostic catheter due to right transradial penetration were excluded. Patients with bilateral RAO and ulnar artery accesses were also excluded. The effect of the learning curve was analyzed each year by comparing the procedural data obtained in the first 20 cases with the other patients. The indication for the interventions was intermittent claudication in 85 patients, and CLI in 110 patients. The Institutional Review Committee accepted the study (SE TUKEB 212/2016) and all patients signed the consent form before the treatment.

4. RESULTS

4.1 Research 1

CDT was technically successful in 74/84 patients (88%), but additional MT and angioplasty and/or stent implantation was necessary in 17 (20.2%) and 45 (53.6%) cases, respectively, to obtain good angiographic results. Clinical success was achieved in 74/84 cases (88%). Procedurally related factors were not statistically different in the subgroups and hospitalization time (15.9 ± 14.5 days vs. 7.7 ± 2.8 days vs. 11.5 ± 6 days) was also not statistically different among the three groups (p=ns).

The cumulative incidence of MAEs at 12 months was 50%. The major amputation rate was 22.6% and the mortality rate 21.5% (regarding patients who have undergone major amputation). Among the major amputations performed, a significant proportion (73.7%) were femoral amputations. Four patients were identified as having

stage IIA according to the Rutherford classification, while 10 had stage IIB. Crural amputations represented 26.3% of the overall number of amputations. Within this subset, four patients were classified as having stage IIA according to the Rutherford classification and one as having stage IIB. The overall rate of stroke was 9.5%: five (5.9%) cases of ischemic stroke and three (3.5%) of hemorrhagic stroke, with a 50% mortality rate. The overall rate of major vascular complication was 9.5% (0%, 11.1%, and 12.1% in the RA, BA, and FA groups, respectively), with a 25% mortality rate.

The adjusted variables used in the Cox regression model used to investigate MAEs and MALEs, which were considered together as the reference model, were entry site, Rutherford stage, target vessel, clinical success, additional procedure, and diabetes mellitus. In all cases, data from the 12-month follow-up period were taken into account during the analysis, and $p<0.05$ was considered statistically significant. Among the adjusted variables examined for MAEs, statistically significant differences were observed for cases of RA penetration (HR, 0.27; 95% CI, 0.07–0.96; p=0.0429).

4.2 Research 2

A second entry gate was used in 30%, 3.3% and 30% of patients in the RA, FA and TP groups ($p<0.01$). Claudication complaints were the indication in 53.3% of patients, CLI in 46.7% of patients.

Technical and clinical success was achieved in 96.6%, 100%, and 100% of the patients in the RA, FA and TP groups, respectively (p=ns). Regarding the procedurally related factors, there

was no significant difference between the subgroups, but the X-Ray dose was significantly lower in the TP group (160.1 vs. 153.1 vs. 63.1 Dyn ($p<0.01$)). The crossover rate was 30% (2/60 case to femoral, 18/60 case to pedal), 3.3% (2/60 case to pedal), and 30% (16/60 to radial and 2/60 to pedal) in the RA, FA, and TP groups, respectively ($p<0.01$). The hospitalization time was significantly lower in the radial group (2.9 vs. 3.45 vs. 3.1 days; $p<0.01$).

The cumulative 6-months MACEs incidence in the RA, FA and TP groups was 5%, 6.7% and 1.7% ($p=0.10$). The cumulative 6-months MALEs incidence in the RA, FA and TP groups was 20%, 16.7% and 10% ($p=0.54$). The major amputation rate was 3.3%, 3.3% and 0.0% in the RA, FA and TP groups ($p=0.55$). The cumulative access site complication rate int the RA, FA and TP groups was 3.3% (0% major and 3.3% minor), 16.7% (3.3% major and 13.3% minor), and 3.3% (3.3% major and 0% minor), respectively ($p=0.01$). The sheath size has not significantly affected the rate of vascular access site complications. Anterograde and cross over approach has been used in 54 (90%) and in 6 (10%) patients. The rate of vascular complications in the anterograde and crossover cases was 10% (2 major (20%) and 8 minor (80%)) and 0% ($p=0.57$).

4.3 Research 3

Technical success was achieved in 188 patients (96.4%), of which the rate was 97.3% (37 of 38 patients) in the DR group and 96.2% (151 of 157 patients) in the PR group ($p=0.9$). Femoral crossover was not necessary in the DR group, while in the PR group it was necessary to switch to FA penetration in 5 cases (3.2%)

(p=0.59). Dual penetration (transradial and transpedal) was required in 14 cases in the DR group (36.8%) and in 28 cases in the PR group (18.9%; p<0.01). There was no significant difference between the two groups regarding radiation dose, fluoroscopy time, procedure time and contrast use.

The complication rate related to the access site was 2.6% and 7% in the DR and PR groups (p=0.46). The only access site complication in the DR group was a minor hematoma, while a >2cm hematoma in the forearm was observed in one patient in the PR group. 6 DR patients (15.7%) and 23 PR patients (14.6%) had MAEs at 6 months. 3 patients (7.8%) in the DR group and 8 patients in the PR group (5.1%) died (p=0.38).

As time progressed, there was no significant difference in either group between procedure times, fluoroscopy times, radiation doses or the amount of contrast after the first 20 cases, despite the high number of complex cases. A significant decrease in fluoroscopy time and contrast amount can be observed over the years, but there was no statistical difference in procedure times and radiation dose. After the first year, the crossover rate was significantly lower for the last 158 patients (p=0.01).

5. DISCUSSION

For the first time in our studies, different approaches (RA [DR and PR], FA, BA, TP) were compared for acute and chronic peripheral lower extremity interventions, focusing on success rates, safety, complication rates related to access sites, outcomes during the

follow-up period, and the significance of the combined use of individual entry sites.

We demonstrated several important findings:

(1) Access site complications were very rare in the RA and TP groups when adequate hemostasis was used, and these were associated with shorter hospitalization period.

(2) DR access was associated with a very low access site complication rate.

(3) FA access is well-suited for patients with poor distal runoff and those requiring dedicated stents, but the access site complication rate is very high.

(4) The crossover rate in the RA and TP groups was significantly higher than in the FA group.

(5) The X-ray dose in the TP group was significantly lower than in the RA and FA groups.

(6) Significant independent predictors of long-term MAEs were determined, with RA access independently associated with a reduced risk of MAEs.

(7) Hybrid approaches can be utilized to reduce the rate of access site complications.

With the development of dedicated interventional tools, the use of alternative access sites has gained increasing importance of endovascular interventions. One such alternative is RA access. The main advantages of RA access include a low complication rate and better patient comfort due to faster mobilization and shorter hospitalization periods. Our study confirmed these findings: the

overall rate of major vascular complications was significantly lower compared to FA access. However, the main disadvantages are the high crossover rate and the difficulty in delivering devices to the target lesion. Due to the decreasing anatomical and technical limitations with the development of the device system, it is now widely used for SFA interventions. Despite advances in device technology, RAO occurred in our study, but it was 0% in cases of ultrasound-guided DR access using a slender sheath. This outcome is likely due to the advantages of DR puncture, which allows for easier compression and ensures adequate hemostasis, resulting in a low incidence of RAO. The biggest technical disadvantage of DR access is the difficulty in delivering guidewires toward the PR artery due to the smaller vessel caliber and acute angulation of the artery. Another limitation of distal puncture is the need for longer instruments; however, in our study, we found no difference in the success of interventions between the PR and DR groups. Ultrasound-guided puncture is recommended to overcome these limitations, as it allows for the determination of vessel size, course, and the severity of atherosclerosis before puncture. Ultrasound guidance was used in all DR puncture cases, facilitating easy anterior single-wall puncture, avoidance of multiple punctures and selection of a disease-free, angulation-free segment. Intraprocedural complications (hematoma formation, dissection, spasm) can also be easily detected.

Antegrade FA puncture is traditionally used during SFA PTAs because it offers a straightforward puncture path and strong backup support when using large femoral devices. If anterograde

puncture is difficult or impossible, crossover contralateral access can be considered, though this approach is sometimes limited by severe calcification, vessel tortuosity, or iliac artery angulation. The main disadvantages of FA puncture, confirmed in our study, are the high complication rate and longer hospitalization time. However, significant improvements in complication rates can be achieved with ultrasound guidance.

The number of TP access procedures has increased in recent years, primarily to treat complex peripheral lesions from a retrograde direction that could not be successfully treated with anterograde access. In our study, we did not observe complications related to TP access, though one patient experienced proximal dissection after stent implantation, which was treated with a drug-eluting stent. The main advantages of TP puncture are the low risk of vascular complications and easy, quick hemostasis.

In addition to alternative access sites, hybrid approaches can reduce the complication rates while maintaining high technical success rate. During SFA interventions, a combination of RA and TP access was effective, though the combined use of BA and FA access was associated with a high vascular complication rate despite ultrasound guidance for FA puncture.

Our study has several limitations worth mentioning. The low number of patients and their uneven distribution across subgroups made it challenging to analyze the entire population. Future studies should account for this and, as the patient population grows, continually reevaluate research findings. Given the beneficial effect

of ultrasound in reducing vascular complications, further comparison of different access sites during peripheral interventions based on standardized ultrasound-guided puncture protocols may be warranted in the future.

6. CONCLUSIONS

Thanks to rapid technical developments in recent years, peripheral PTAs have expanded alongside coronary interventions. Our study, which forms the basis of this thesis, concludes that both acute and chronic lower limb peripheral vascular diseases can be safely and effectively treated with RA, FA, BA, and TP access, but RA and TP access are associated with a lower complication rate and shorter hospitalization period. This rate can be further reduced by using hybrid access techniques. Despite the higher complication rate, FA puncture remains a viable option, especially in patients with severely diseased outflow tracts who require dedicated stents and other large-caliber devices. The potential advantages of alternative access sites can be most effective when chosen and applied with appropriate indications and careful consideration of potential complications and their solutions.