Original Article



The Treatment Role of Anti-aggregants and Anti-coagulants in Radial Artery Occlusion after Transradial Coronary Angiography

Transradial Koroner Anjiyografi Sonrasında Gelişen Radial Arter Trombozunda Anti-agregan ve Anti-koagülan Tedavilerin Rolü

ABSTRACT

Objective: The transradial approach (TRA) has been widely used for coronary procedures. The rate of complications such as bleeding, hematoma and pseudoaneurysm is reduced with TRA. The purpose of this study is to search the treatment role of anti-aggregants and low molecular weight heparins (LMWH) in situation of radial artery occlusion (RAO).

Methods: A total of 239 patients (140 men, 58.6%) were included. Of the patients 159 (66.5%) were elective, and 80 (33.5%) had acute coronary syndrome. When RAO was detected, patients were treated with 2 weeks of LMWH.

Results: In 23 (9.6%) of 239 patients, RAO was observed. From the 23 patients with RAO, 12 (52.8%) were using anti-aggregants, and the remaining 11 (47.8%) did not use. In terms of RAO, a statistically significant difference was observed between antiaggregant users and non-users (p<0.001). In the group using antiaggregants and LMWH a statistically significant improvement was observed in the radial flow compared with the group treated withLMWH alone (p<0.001).

Conclusion: In the present study, we showed that the addition of anti-aggregants to anti-coagulants decreased RAO rate, declined the symptoms of RAO, also potentiated the effects of anti-coagulants and resulted in better recanalization rate of RAO

Keywords: Transradial angiography, radial artery occlusion, low molecular weight heparin, anti-aggregant

ÖZ

Amac: Transradival vaklasım (TRY) koroner girisimlerde yaygın olarak kullanılmaktadır. TRY ile kanama, hematom ve psödoanevrizma gibi komplikasyon oranları azaltılmaktadır. Bu çalışmanın amacı anti-agreganların ve düşük moleküler ağırlıklı heparinin (DMAH) tedavideki rolünü ortaya koymaktır.

Yöntemler: Toplam 239 olgu [140 erkek, (%58,6)] dahil edildi. Olguların 159'u (%66,5) elektifti ve 80'inde (%33,5) akut koroner sendrom vardı. Radiyal arter oklüzyonu (RAO) saptanan hastalar 2 hafta DMAH ile tedavi edildi.

Bulgular: Hastaların 23'ünde (%9,6) RAO gözlendi. RAO gelişen 23 olgudan 12'si (%52,8) anti-agregan kullanıyordu, 11'i (%47,8) kullanmıyordu (p<0,001). Anti-agregan kullanan grupta, DMAH tedavisi sonrası radial akımda sadece DMAH tedavisine kıyasla istatistiksel olarak anlamlı bir iyileşme gözlendi (p<0,001).

Sonuç: Bu çalışmada anti-agreganların anti-koagülanlara eklenmesinin RAO oranını ve, semptomlarını azalttığını ve ayrıca anti-koagülanların etkilerini güçlendirdiğini ve RAO'da daha yüksek rekanalizasyon oranı ile sonuçlandığını gösterdik.

Anahtar Sözcükler: Transradiyal anjiyografi, radyal arter tıkanıklığı, düşük moleküler ağırlıklı heparin, anti-agregan

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Introduction

Coronary angiography (CAG) is still the gold standard diagnostic method of coronary vascular occlusion (1).

The transradial approach (TRA), which is widely used in coronary and neuroendovascular procedures, is increasingly becoming the default procedural pathway due to early mobilization, discharge, cost, and patient comfort (hildick) (1). The success rate increases with the use of appropriate equipment and increased experience (2,3).

TRA has few complications: Hematoma of forearm, radial artery pseudoaneurysm, spasm and occlusion (4,5). Radial artery occlusion (RAO) occurs due to endothelial damage leading to thrombus formation and occlusion (6). The rate of RAO varies from center to center, ranging from 5% to 30% (7-9), which may result from the subtle nature of RAO. RAO is mostly silent and asymptomatic. The patency of the radial artery is important for several reasons, as future interventions may be required for arterial conduit bypass and fistula for dialysis. Various efforts have been made to prevent RAO, such as increasing the dose of heparin administered, patent-hemostasis, distal radial approach, etc. (10-15). TRA has been practiced for decades, and since RAO is a well-known complication, definitive treatments have not been established so far. Anti-coagulant treatment, the standard treatment for RAO, has been studied in small trials.

After RAO, treatment with low molecular weight heparin (LMWH) for 2-4 weeks is associated with increased radial artery patency in the absence of critical limb ischemia (zankl ar, Shroff A) (5,16). Despite many precautions and efforts, RAO does occur. In this study, we examined the role of anti-aggregant and LMWH in treatment after RAO.

Methods

This study was performed at a high-volume cardiac center. It was approved by the local ethics committee (16/76 and 03 September 2019). All the patients involved were informed about the study and their consent was obtained.

The patients with acute coronary syndrome (ACS) and stable angina who were admitted to our clinic with the indication of coronary angiogram (CAG) were included in the study. The mean age of the patients was 61.7 (±10.3) years and 140 (58%) of 239 patients were male. Of the 239 patients included in the study, 159 (66%) were elective and 80 (34%) had ACS. Complete blood count, electrocardiogram (ECG), blood sugar, blood urea nitrogen, creatinine, serum electrolytes, and cardiac enzyme (troponin, CK-MB) were evaluated in all patients as recommended for routine clinical evaluation in coronary artery disease guidelines. They had dynamic ST-T wave changes with typical chest pain on the ECG, and cardiac enzyme levels were detected more than 5 times at the time of admission and were accepted as ACS (16). The patients with metabolic imbalance, chronic kidney disease, and those receiving chemotherapy for cancer were excluded from the study. For TRA, the left radial artery was used. Allen's test and digital pulse oximetry were

performed before angiography, and those who passed both tests underwent radial angiography and were followed up. Local anesthesia was applied to the region to be intervened by placing the left hand in the extension and external rotation position. For the local analgesics 0.5 cc Prilocaine (CITANEST® 2%) was used subcutaneously. Then, intra-arterial puncture was performed with a 20 G puncture needle, after arterial pulsation 45 mm 0.025 "non-flonized wire and a radial sheath of 6F 15 cm (TERUMO 6 F)" were placed without resistance over the wire. Before diagnostic CAG, 100 mcg perlinganit and 2500 U unfractionated heparin were diluted in the sheath. During the procedure, the patients with radial spasm were excluded from the study. A J-tip wire with a diameter of 0.035 inches from 6F radial sheath was easily inserted to the arch aorta, then 6 F metronic brand JL 3,5-4-4,5 and JR 4 coronary diagnostic catheters were used for diagnostic CAG. During CAG, the patients with normal coronary arteries were not administered anti-aggregants. A dose of 100 IU/kg of heparin was administered to the patients with stenosis over 70% and who were scheduled for stent surgery in the same session. A terebund was used to close and control bleedingafter CAG. Elective patients were given clopidogrel and acetylsalicylic acid (ASA) dual anti-aggregants per guideline recommendations, and some of the patients with ACS were given ASA plus clopidogrel or ticagrelor plus ASA.

Only ASA treatment was given to the patients with non-critical plaque in the coronary arteries. Patients who were discharged without any problem were called for control after 48 hours, and radial pulse examination was performed. Radial artery flow pattern was checked with superficial USG in the patients with no radial pulse and/or painful symptoms in the radial region. Patients who were detected as having radial occlusion with USG were administered subcutaneous LMWH (enoxaparin) in the morning and evening for 14 days, depending on their weight. Following two weeks of LMWH treatment, the flow was evaluated by radial USG.

Statistical Analysis

The SPSS 16.0 for Windows software was used for software analysis of the data. Numerical values were given as mean \pm standard deviation, and categorical variables as percentage (%). Categorical variables among the groups were compared using the chi-square test. Measurement variables were given as mean \pm standard error and a two tailed p<0.05 value was considered statistically significant.

Results

A total of 239 patients, 140 (58.6%) of whom were male, were included in this study. Two patients who failed the Allen and pulse oximetry tests were excluded from the study. In 5 patients after sheath insertion, significant radial spasm occured. Additionaly in 4 patients, the radial artery was previously used as a conduit for bypass grafting. Femoral approach was applied to all 11 patients and all were excluded from the study. Baseline clinical and demographic characteristics of the patients are shown in Table 1. There was no statistical difference between the subgroups in terms of general characteristics.

The demographic characteristics of the patients in the angiography laboratory are summarized in Table 2. Stable angina pectoris was the indication for CAG in 159 patients and 80 patients had ACS. Interventional procedure was performed in 84 (35.1%) patients.

Ultrasonographic characteristics of RAO within 48 hours are shown in Table 3.

All the patients were called for control 48 hours after discharge and their radial pulse was re-examined. RAO was detected in 23 of 239 patients (9.6%) within 48 hours. In 42 (17.6%) patients who were discharged, there was no lesion on CAG and no antiaggregant or anti-coagulant was prescribed. While 12 (52.8%) of 23 patients with RAO used anti--aggregant, the remaining 11 (47.8%) did not use any.

Table 1. Basic clinical and demographic characteristics ofpatients at the time of admission			
	Patients (n=239)		
Age	61.7±10.3		
Gender M, (n, %)	140 (58.6)		
Obezity (n, %)	99 (41.4)		
Hypertansion (n, %)	147 (61.5)		
Hyperlipidemia (n, %)	60 (25)		
Diabetes (n, %)	110 (46)		
Smoker (n, %)	105 (44)		
Family history (n, %)	29 (12)		
BMI	28.3±3.6		
ECG NSR (n, %)	215 (90)		
AF (n, %)	24 (9.6%)		
Coronary angiography			
Electively (n, %)	159 (66.5)		
Diagnostics (n, %)	141(59)		
Interventional (n, %)	18 (7.5)		
Urgent (n, %)	80 (33.5)		
Diagnostics (n, %)	14 (5.9)		
Interventional (n, %)	66 (27.6)		
Medication			
Anti-agg and anti-coagulant (n, %)	197 (82.4)		
ASA	55 (23)		
Klopidogrel	7 (2.9)		
ASA and klopidogrel	83 (34.7)		
ASA and ticagrelol	29 (12.1)		
Warfarine	10 (4.2)		
Rivaroxoban	13 (5.4)		
Without medication (n, %)	42 (17.6)		
BMI: Body mass index, ECC: Electrocardio	aram NSP: Normal sinus thythm AF		

BMI: Body mass index, ECG: Electrocardiogram, NSR: Normal sinus rhythm, AF: Atrial fibrillation, anti-agg: Anti-aggregant, ASA: Asetilsalicylclic acid

A comparison was made between two groups using and not using anti-aggregants. A statistically significant difference was observed in terms of RAO between the two groups that received and did not receive anti-aggregant treatment (p<0.001). While all the patients with RAO who did not use anti-aggregants had pain in the radial intervention area, symptoms were observed in 5 (31.2%) patients using anti-aggregants, and a statistically significant difference was observed between the two groups (p<0.001).

All the patients with RAO received a two-week course of LMWH based on their weight. Symptomatic improvement was observed in the entire LMWH-treated group and no invasive or surgical procedure was required. There was a statistically significant improvement in radial flow after LMWH treatment in the antiaggregant-using group compared to non-users (p<0.001) (Tables 4, 5). During the follow-up period, no significant bleeding and related complications were observed in all the groups.

Table 2. Demographic characteristics of patients duringangiography laboratory				
Coronary angiography				
Electively n, (%)	159 (66.5)			
Diagnostics n, (%)	141(59)			
Interventional n, (%)	18 (7.5)			
Urgent n, (%)	80 (33.5)			
Diagnostics n, (%)	14 (5.9)			
Interventional n, (%)	66 (27.6)			
Systolic blood pressure (mmHg)	133.8±16.5			
Diastolic blood pressure (mmHg)	74.3±8.1			
Heart rate/min	74.4±11.2			
Procedure time/min	39.2±8.9			
Unfractionated heparin dose/U	4,439±2,640			
Thera band follow time/min	153±18			

Table 3. Ultrasonographic characteristics of radial artery occlusion (RAO) at baseline

	Patiens using anti- plt(s) (n=174)	Patient not using antiplt (n=42)	Ρ
Radial artery occlusion (n, %)	12 (52.8%)	11(47.8)	0.001
Complete oclusion	9 (75%)	8 (72.7%)	ns
Partial occlusion	3 (25%)	3 (27.3%)	ns
Extent of hematoma (n, %) Distal of forearm	1 (6.7%)	1 (12.5%)	ns
Complete forearm	0 (0.0%)	0 (0.0%)	ns

	Patients using anti-aggregants (n=12)	Patients not using anti-aggregants (n=11)	Ρ
Recanalization (n, %)	7 (63.6)	4 (36.4)	0.001
Partial recanalization	2 (28.6)	4 (36.4)	ns
Complete recanalization	5 (71.4)	0 (0.0)	0.01
Persistent hematoma (n, %)	0 (0.0)	0 (0.0)	Ns
Neurological symptoms (n, %)	0 (0.0)	0 (0.0)	Ns
Persistence of symptom	0 (0.0)	0 (0.0)	Ns

Table 4. Ultrasonographic characteristics of radial artery occlusion after treatment with low molecular weight heparin

Table 5. The clinical effect of anti-aggregant therapy

	RAO n=23 (9.6%)	Ρ	Symptomatic n=16 (6.7%)	Ρ	Successful radial flow after LMWH n=11(4.6%)	Ρ
Anti-aggregant users n (%)	12 (52.8)		5 (31.2)		7 (63.6)	
Non-users of anti-aggregant n (%)	11 (47.8)	0.001	11 (68.8)	0.001	4 (36.4)	0.001

Discussion

In this study, we showed that the use of anti-aggregants following CAG significantly reduced the development of RAO and also alleviated symptoms if thrombosis occurred. We also found that a two-week LMWH treatment for RAO was effective in recanalizing the thrombosed arteries. In patients with RAO, anti-aggregant therapy increased the efficacy of LMWH without increasing bleeding frequency.

Since prevention is better than treatment, there have been many efforts to prevent RAO. The main approach to reduce RAO is heparin dose. At the start of TRA, lower doses (1,000 IU) of heparin appeared to be associated with a 30% rate of RAO (17). Over time, the dosage has increased. In a large meta-analysis, it was shown that the standard dose of heparin (5,000 IU) resulted in a reduction of RAO compared to the lower dose (2,500 IU) (18). Also, in another randomized study, high heparin dose (100 IU/kg) compared to standard heparin dose (50 IU/kg) was shown to significantly reduce RAO (8). In the present study, we used lower dosage of heparin (2,500 IU) in all the groups. In the previous studies, the average rate of RAO was about 6% (8,9). In the present study it was about 10%. The rate of RAO in our study is slightly higher than the previous studies. This is probably a result of the lower dosage of the heparin used in the present study. Another possible risk factor of RAO is the sheath size. There are various studies showing different results. The main tendency was that the risk of RAO decreased as sheath size did (13). However Hahalis et al. (15) demonstrated in a metaanalysis that the risk of RAO was not different between sheath sizes. They concluded that the higher dose of heparin, rather than sheath size, likely neutralized the larger sheath size. In the present study we used 6F sheath in all the patients. Therefore, we cannot draw any conclusions about the effect of sheath size on the RAO. Another attempt to prevent RAO is distal TRA (4,14). Although distal TRA has been shown to be safe, classical TRA is widely used for CAG and intervention due to its small size. The result of distal TRA needs further investigation. In the present study we performed a regular TRA.

The duration of the procedure is claimed to be another factor for RAO (15). It was thought that the risk of RAO increased as the duration of the procedure was prolonged. However, a meta-analysis did not show any difference between diagnostic and interventional CAG, which might be due to additional heparin administration in prolonged procedures. In the present study we also did not find any difference between diagnostic and interventional groups.

One of the suggested approaches to reduce RAO is to perform patent hemostasis instead of occlusive. A large meta-analysis comparing the results of 94 studies found no significant difference in overall RAO between occlusive or patent hemostasis (15).

In our institution, we use patent hemostasis. Since we did not use occlusive hemostasis, we could not reach any conclusion about the type of hemostasis. Patients with RAO have few treatment options.

In early 2000, Geschwind et al. (19) studied thrombolytic treatment for critical limb ischemia, which was now considered an aggressive treatment.

In the case of critical limb ischemia, which is a rare condition today, percutaneous recanalization or surgical resolutions are preferred in appropriate patients (19,20). Another widely accepted and applied treatment for RAO is anti-coagulation.

In the Leipzig prospective vascular ultrasound registries, Uhlemann et al. (13) studied the treatment effect of LMWH alone for 7 to 14 days with dual anti-aggregants in patients with symptomatic RAO. A half dose of LMWH was given when the patients took dual anti-aggregants. They determined that 7 days of treatment with LMWH resulted in a recanalization rate of 31.5% in RAO. In persistent RAO, they extended treatment up to 14 days, showing recanalization rate of 55.6% in the LMWH group. Similar to that study, in the present study, a 2-week treatment of LMWH with a single anti-aggregant resulted in a rate of 64% recovery in radial arterial flow. Different from the Leipzig registry, we gave full dose of LMWH to all patients. Zankl et al. (21) studied the effectiveness of the LMWH. They showed that after RAO developed, treatment with LMWH for 4 weeks was associated with better patency and symptomatic relief of RAO. In another study, Bernat et al. (22) tried transient occlusion of ulnar artery for one hour in order to increase flow to radial artery and recanalization. They performed the procedure within 3-4 hours of the diagnosis of RAO. They found that recanalization of the radial artery was significantly increased. Recently, 4 patients with RAO were treated with the new oral anti-coagulant apixaban (23). They found that all four patients were successfully recanalized after 1 month. In this study, we showed that RAO was significantly more recanalized after 2 weeks of LMWH treatment. We indicated that the post-procedure RAO rate was significantly lower in patients receiving antiaggregants. Additionally, we also found that the combination of anti-aggregant and LMWH provided better recanalization.

The addition of anti-aggregant strengthens the effect of LMWH. Also patients taking anti-aggregants have less symptoms. We may suggest that anti-aggregants and anti-coagulants block all the pathways of thrombosis and coagulation. As a result, the endothelial fibrinolytic system gains time for recanalization. In a case control study, Rammos et al. (24) studied the efficacy of anti-coagulation (LMWH, or novel oral anti-coagulants) alone or with vasoactive alprostadil in patients with RAO. They found that the addition of vasoactive medication had no role in regaining of the radial artery patency. They concluded that anticoagulation was the main treatment of RAO. In a recent study, Steinmetz et al. (20) divided the patients with RAO into two groups, treating them with anti-aggregants or anti-aggregants plus anti-coagulants (LMWH, vitamin K antagonists or novel oral anti-coagulants). They determined that after 3 months of treatment, anti-coagulation plus anti-aggregants significantly resulted in more complete and partial reopening of the radial artery rather than anti-aggregants alone. In the present study, we gave anti-aggregants plus anti-coagulants or alone anticoagulants. We found better resolution of RAO and better symptom improvements in the patients treated with anti-aggregants plus anti--coagulants.

In previous studies, the recanalization rate was reported between 55 to 87% depending on the duration of treatment (9,15). When anti-coagulation therapy was extended to one month, the recanalization rate increased significantly. In the present study, we treated RAO for 2 weeks. The success rate was 64%. We recommend that anti-coagulants be given for at least one month after the diagnosis of RAO.

Study Limitations

This study has several limitations. First, this was a single center study. The results could not be generalized because the procedures were handled by limited experts. All the patients were treated with 6F sheath. We did not evaluate other sheath sizes. The rate

of RAO could be different when different sheath sizes were used. Another limitation was that we evaluated the RAO rate one day after TRA. There could be late RAOs, which we did not evaluate. After performing the cocktail solution we did not evaluate the anti-coagulation time in diagnostic procedure. We did not have an ulnar artery occlusion effect on the RAO. Finally, we gave two weeks of anti-coagulation. We did not evaluate patients for more than two weeks. The recanalization rate could be better after two weeks of treatment.

Conclusion

In this study, we showed that although RAO was still a problem, the addition of anti-aggregants to anti-coagulants reduced the rate of RAO and the symptoms, and also potentiated the effects of anti-coagulants, resulting in a better recanalization rate of RAO. Randomized clinical trials are needed for better clinical advice.

Ethics

Ethics Committee Approval: This study was performed at a high-volume cardiac center. It was approved by the local ethics committee (16/76 and 03 September 2019).

Informed Consent: All the patients involved were informed about the study and their consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.N., M.U., Design: A.N., M.U., Data Collection or Processing: A.N., M.U., Analysis or Interpretation: A.N., M.U., Literature Search: A.N., M.U., Writing: A.N., M.U.

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