

Heparin Low Doses and Standard Doses Effect on Trans-Radial Catheterization

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ABSTRACT

Background: Transradial artery is being utilized by an expanding number of interventional cardiologists to perform percutaneous interventions. Nevertheless, occlusion of radial artery (RAO) is prominent after transradial (TR) catheterization. Use of anticoagulant drugs is one way to prevent RAO. The conventional dose of heparin is (2000IU-3000IU or 50IU/kg) and high-dose is (5000IU or 100IU/kg). The use of high-dose heparin and standard-dose heparin is still debatable.

Objective: The present study will analyze the non-randomized controlled trials of standard and high dose of heparin for the prevention of radial artery occlusion after transradial catheterization.

Methodology: A prospective double-blinded non-randomized controlled trial was carried out. Demographic data related to socio-economic status such as their age, occupation, gender, and smoking habits were collected. Grouping was done so that patients may either be placed in group 1 which will receive 2500UI or into group 2 which will get 5000UI of unfractionated heparin. RAO was the key endpoint of our study. Major bleeding, hematomas and radial artery spasm were secondary outcome measure.

Results: 471 patients were made part of this study. 235 patients were placed in group A which received 2500IU and 236 were placed in group B which received 5000IU. RAO was noted to be significantly higher in the group the received the standard dose of UFH as compared to the group that received high dose UFH (8 % vs. 3.3 %, $p = 0.005$). Female gender (OR: 2.951, 95% CI: 1.57-5.46, $p = 0.002$), hypertension (OR: 0.02, 95% CI: $p = 0.005$ and standard dose UFH (OR: 2.822, 95% CI: 1.343 – 5.911, $p = . 0.007$) were found to be the independent predictors of RAO.

Conclusion: Weight-adjusted higher dosage of UFH in TRA for diagnosis yielded remarkable results in reducing the rates of early RAO against the standard administered dosage

INTRODUCTION

Cardiovascular disease (CVD) causes 80% – 86% deaths in countries that have low and middle incomes and is considered as major cause of deaths worldwide.¹⁻⁴ Availability of non-invasive and invasive treatments alongside primary and secondary approaches related to prevention of CVD has contributed in terms of reducing the overall mortality in first world nations.⁵ In 1989, Campeau et al introduced transradial coronary angiography to diagnose CVDs.⁶ While stenting and coronary angioplasty using TRA or transradial approach was first documented by Kiemeneij et al. in 1993.⁷ The most commonly implemented method for providing interventions and coronary angiography remains to be TFA or transfemoral approach and radial artery is being utilized by an expanding number of interventional cardiologists to perform percutaneous interventions.⁸⁻¹¹ Moreover, numerous studies signify the benefits of TRA as its success rates are high in general and overall satisfaction of the patients and their comfort is also high while there is relatively a lower potential of bleeding at the access site.¹²⁻¹⁷ Despite unique advantages, the complications of trans-radial catheterization are still present. For instance, Radial artery occlusion, forearm hematoma formation, compartment syndrome, radial artery perforation, and pseudoaneurysm. Nevertheless, occlusion of radial artery (RAO) is prominent after transradial(TR) catheterization.¹⁸⁻²⁰ Following the interventions and coronary angiography, the associated rate of RAOs is still debated to vary between 0% – 30.5% considering some recent studies.²¹⁻²⁹ And rates were noted to be 0% – 13.9% particularly after coronary angiography.²⁶⁻²⁹ Many other secondary complications arise after RAO, like the inability of the interventionist to reuse the artery vessel and shortage as a graft for coronary artery bypass surgery.³⁰⁻³¹ There are many possibilities to prevent the radial artery occlusion RAO, the conservative method is using the gentle and skilled technique for avoiding damage to the radial artery during the preoperative perforation process. Other prevention techniques are rational such as, use of anticoagulant drugs, the use of non-obstructive hemostasis, the reduction of compression

hemostasis time, preoperative injection of nitroglycerin and reasonable pain relief.^{25, 32}

The selection of dose of heparin in coronary angiography depend on the calculation of patients' weight and added to complete heparinization and is not clearly determined yet.³³ The most commonly used doses of heparin are 2000IU – 5000IU to prevent the complication of RAO for coronary angiography. The conventional dose is (2000IU-3000IU or 50IU/kg) and high-dose is (5000IU or 100IU/kg). A number of studies establish an association linking RAO and the dosage of heparin. Nevertheless, the use of high-dose heparin and standard-dose heparin in transradial coronary angiography to efficiently prevent the incidence of RAO without increasing the risk of bleeding and other associated issues are still debatable. Furthermore, there is a lack of research comparing the clinical effects of these 2 doses of heparin in Pakistan. The present study will analyze the non-randomized controlled trials of standard and high dose of heparin for the prevention of radial artery occlusion after transradial catheterization

METHODOLOGY

Study Design, duration and setting: The prospective double-blinded non-randomized controlled trial was carried out at department of cardiology at name of center from month/year to month/year over a 1-year duration. To select the patients, we used the method of non-probability consecutive sampling. Patients over the age of 18 years, had a negative Allen's test, were directed for coronary catheterization by radial access and consent about their participation in our study were set as the criteria for inclusion in our study. Patients that were subjected to chronic renal failure, referred an angiography or angioplasty on an urgent basis, had a radial PCI before, had bleeding disorders, or pathological Allen tests, were not made part of our study. An approval was acquired from the institutional ethics committee about the study alongside written consents from the subjects after they had been provided information.

Pre-procedural protocol: All the patients that were part of our study went through clinical examination and their medical history was obtained. Demographic data related to socio-economic status such as their age, occupation, gender, and smoking habits were collected by a physician from the treatment group. Medical records like acute coronary syndrome, risk factors associated with CVD such as presence of diabetes, use of relevant medications and occurrence of peripheral vascular disease were acquired by the physician. Standard means were employed for the measurements of weight and height of the patients. Calculation of BMI was done by dividing the weight of the patients by their height squared (kg/m²). Through a mercury sphygmomanometer, a trained nurse took the blood pressure of the patients following a standard protocol³⁴ that is to take the reading when the patient is in sitting position and to take it twice from the left and right arms providing a rest of 5 minutes.

Transradial catheterization procedure: In sterile conditions, an injection of 2% lidocaine was administered to achieve anesthesia. A needle of 20-gauge was utilized to puncture the site of radial artery which is present 2-3 cm adjacent to the wrist's crease. When a pulsatile flow appeared, a wire measuring 0.025 inch was proceeded into the radial artery lumen. After the removal of the needle, a hydrophilic sheath measuring 6-Fr short (7 cm) was inserted over the guidewire. After the insertion of the sheath, a vasodilator (5 mg of verapamil or 100 µg of nitroglycerin) was provided to the subjects and heparin (2,500 or 5,000 U) which was diluted beforehand in a syringe measuring 10-ml, was given to the patients afterwards in the injection form in their radial artery.

Grouping was done so that patients may either be placed in group 1 which will receive 2500UI or into group 2 which will get 5000UI of unfractionated heparin administered by another staff member that was not aware of the medical history of the patients.

As soon as the procedure ended, radial sheath was removed immediately as well as a radial compression device known as TR Band (Terumo, Tokyo, Japan) was used at the site of access and which was filled by 15ml of air. 2ml air was removed periodically after every 15 mins from the balloon of the TR Band followed by its removal after 1 hour.

Within the period of 3-4 hours after their cardiac catheterization, the patients were given discharge from the hospital. Before their discharge, all the patients were observed for local swelling, hematoma, pain, absence of pulse, and weakness. 7 days following their cardiac catheterization, all patients were subjected to reevaluation using Doppler ultrasonography and physical examinations.

Study endpoints: After the removal of TR Band and maintaining their hemostasis, discharged was given to all the patients. RAO was the key endpoint of our study. Major bleeding, hematomas and radial artery spasm were secondary outcome measure.

The patients were clinically examined by radial pulse palpation. Radial artery occlusion (RAO) was considered as the loss of radial pulse on palpation, validated by loss of audible blood flow sound across the radial artery examined through portable hand-held doppler and the Doppler ultrasonography was used to perform radiological examination.

Hematoma and hemorrhage were described as swelling at a localized region accompanied by bruising and active bleeding at the site where sheath was inserted. Five signs were noticed to define radial artery spasm: i) unceasing pain the forearm, ii) painful response whenever catheter was manipulated, iii) painful response when the catheter is withdrawn, iv) difficulty in manipulation of introducer sheath or catheter after getting trapped by the radial artery v) substantial resistance felt when the introducer sheath was withdrawn. When at least 2 out of these 5 signs were present, we declared the presence of radial artery spasms.

Major bleeding was defined as when a transfusion of more than 2 units of blood was required

Statistical analysis: SPSS version 20 was used to perform all the statistical analysis. For the categorical variables, the data were presented as percentages and for continuous variable, means

were presented with standard deviations. Non-normally distributed variables were expressed as median (IQR). To compare the continuous variables student's t-test was used. We used Chi-square test to evaluate categorical variables. For the determination of independent predictors of RAO, we used Multivariate logistic regression analysis. All the probabilities were by nature two-tailed and p values of less than 0.05 were deemed significant statistically.

RESULTS

471 patients were made part of this study. Out of those 471 patients, 65.2% were male while the mean age was analyzed to be 58 years. 235 patients were placed in group A which received 2500IU and 236 were placed in group B which received 5000IU. Disease history along with laboratory features, clinical, demographical and procedural characteristics of the study population are summed up in Table 1. No significant difference was noted regarding the baseline characteristics and comorbidities between the group with higher doses of unfractionated heparin (UFH) and the group receiving standard doses of UFH

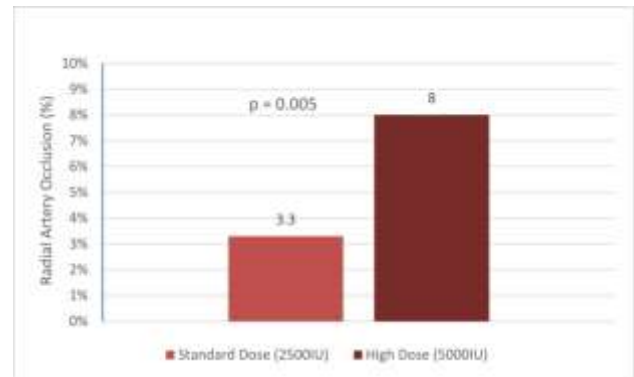


Figure 1: Comparison of RAO between standard and high dose groups

Periprocedural adverse events pertaining to the groups under study are listed in Table 3. Between the group receiving higher dose of UFH and the group receiving standard dose, hematoma yielded indifferent results i.e. (4.6% vs. 3 %, p = 0.60). Only one of the patients in the group with high UFH reported major bleeding. Rate of the RAS was similar in both the study groups as well where RAS in standard group was at 8.5% while it was noted to be at 10% in the group with high dosage UFH whereas p = 0.51. RAO was noted to be significantly higher in the group that received the standard dose of UFH as compared to the group that received high dose UFH (8 % vs. 3.3 %, p = 0.005, Figure 1)

Table 1: Baseline demographic, clinical and angiographic characteristics

Variable	Group 1 n = 235	Group 2 n = 236	p-value
Gender Female, n (%)	97 (41.2 %)	89 (37.7 %)	0.43
Age, years	58.1 ± 10.6	59.2 ± 10.7	0.18
BMI, kg/m ²	27.1 ± 3.5	26.9 ± 3.9	0.25
Diabetes mellitus	75 (31.9 %)	85 (36 %)	0.17
Hypertension	114 (48.5 %)	107 (45.3 %)	0.41
Smoking	90 (38.2 %)	101 (42.7 %)	0.36
Previous CAD	72 (30.6 %)	84 (35.5 %)	0.29
Number of catheters (mean ± SD)	1.11 ± 0.31	1.15 ± 0.38	0.27
Fluoroscopy time (min) (mean ± SD)	8.21 ± 0.71	8.22 ± 0.46	0.06
Heparin doses, median (IQR)	3760 (3400 – 4000)	7100 (6550 – 8000)	< 0.001
Triglycerides (mg/dL)	159 ± 69	159 ± 65	0.98
HDL- cholesterol (mg/dL)	41 ± 9.1	38 ± 9.1	0.10
LDL- cholesterol (mg/dL)	112 ± 33	77 ± 12	0.18

Multivariate logistic regression analysis revealed the independent predictors of RAO (Table 3). Female gender (OR: 2.951, 95% CI: 1.57-5.46, $p = 0.002$), hypertension (OR: 0.02, 95% CI: $p = 0.005$ and standard dose UFH (OR: 2.822, 95% CI: 1.343 – 5.911, $p = .0007$) were found to be the independent predictors of RAO

BMI: Body mass index, CAD: Coronary artery disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation

Table 2: Peri-procedural complications of the participants

Variable	Group 1 n = 235	Group 2 n = 236	p-value
Radial artery occlusion, n (%)	19 (8 %)	8 (3.3 %)	0.005
Hematoma, n (%)	7 (3 %)	11 (4.6 %)	0.60
Major bleeding, n (%)	0 (0 %)	1 (0.4 %)	-
Radial artery spasm n (%)	20 (8.5 %)	24 (10 %)	0.51

Table 3: Independent predictors of RAO in multivariate analysis

Variable	Odds ratio	p-value	95% CI
Female Gender	2.951	0.002	1.57 – 5.46
Age	0.991	0.61	0.961 – 1.020
BMI	1.079	0.12	0.981 – 1.189
Hypertension	0.023	0.005	0.003 – 0.309
Standard heparin dose	2.822	0.007	1.343 – 5.911
Fluoroscopy time	0.989	0.08	0.991 – 1.002

DISCUSSION

In our study we investigated the link of RAO with high dose UFH in comparison with standard dose UFH and the incidence of RAO after radial access coronary angiography providing 2500 IU vs 5000 IU injectable heparin. Occlusions of TRA access are often found to produce no symptoms and as a result remain underdiagnosed. Due to this, a logical approach seems to be on dealing with these events is to use an anticoagulant therapy.³⁵

In the current study we demonstrated that hypertension, dose of heparin and age to be independent predictors of RAO. Lower rates of RAO were independently related with high dose UFH without elevating minor or major bleeding.

On a global scale, TRA is gaining popularity as being the strategy of choice for cardiac catheterization crediting to its comfort level for patients, early discharge and mobilization for the patients, low bleeding at the site of access and simple achievement of an effective hemostasis. Modern guidelines accentuate on TRA being the first approach for cardiac catheterization as it is linked with better clinical outcomes.³⁶

Nevertheless, challenges and complication do arise in TRA. TRA in general is considerably more technically difficult than the femoral approach as it requires use of several specific catheters, problems during access, tortuosity of subclavian artery, RAS, abnormalities of anatomy related to radial and brachial artery, increased time to complete the procedure and severe pain additionally it takes up a longer duration to learn as well.³⁷

The most critical complication associated with TRA is RAO as RAO shows no symptoms and with techniques and time of evaluation of RAO showing such diversity in the literature, its rate of incidence is widely diversified ranging from 0% and extending up to 30.5% with the average being 10%.³⁸ RAO rates are reportedly higher right after the procedure but see a constant decline with the course of time crediting to the spontaneous recanalization where rate of incidence for the early RAO within 24 hour period decrease from 7.7% to 5.5% at 1 month.³⁹⁻⁴⁰ In addition to that, an absent radial artery pulse promotes underdiagnosis of RAO.³⁹ Thus, Doppler ultrasound provides an in-depth objective information related to RAO by determining blood flow using a colour Doppler and providing structural imaging of the arteries.^{30, 40} Our study made use of Doppler ultrasound to diagnose RAO and found it to be present in 36 (5.7%) of the subjects at the 7th day of them after being subjected to cardiac catheterization. We found the ratio in our study to be inline with the data previously reported in literature.^{30, 41}

Numerous parameters such as BMI, sex, co-morbid conditions such as diabetes mellitus and hypertension including some peri-procedural variables that include ratio of artery with respect to the sheath, compression duration and use of heparin have been investigated so that causes of RAO can be explained.⁴¹⁻⁴³ Many studies have been done on the optimal doses of heparin for the prevention of RAO and they support the idea to administer at least 50IU/kg up to 5000 IU UFH through interatrial means.⁴⁴⁻⁴⁶ In the current study, RAO was found to be significantly lower in the patients receiving high dosage of UFH compared against the group that received standard dosage. Besides that, we found standard dose of heparin to be an independent factor for the increase in RAO by 2.8 folds. Furthermore, increased dosage of heparin was correlated with 65% reduction in the risk of RAO. The obtained results pertaining the use of high dosage of anti-coagulations were inline with the results of prior studies which outline the benefits of high dose anti-coagulations for the prevention or RAO in patients who are undergoing cardiac catheterization.⁴⁷⁻⁴⁸ Thus it can be said that the use of high dose of UFH in patients undergoing cardiac catheterization is a reasonable choice.

Risk of RAO in women after TRCAG is found to be higher contributed by their short body stature.⁴⁹ In our study we found women's risk for RAO to be greatly increased, female gender reported as independent predictor of RAO.

A study by Buturak et al. associates hypertension with radial artery patency following TRCAG.⁵⁰ Our findings that hypertension is another

independent predictor of radial artery occlusion was in accordance with their findings. This may be attributed to the increased stiffness of the artery which may prevent complete disruption of the flow in the artery during compression and provides better conditions for a good patent hemostasis.

Our study has a number of limitations. First, our study was based on a single centre and the size of the study sample was small. Other than that, we did not account for the dimensions of radial artery by ultrasonography prior to catheterization thus an estimation for sheath to artery ratio could not be made. To examine the impact of the diameter of radial artery on the rate of RAO would contribute further in this study. Rate of RAO was calculated after 7 days of cardiac catheterization. Follow up duration longer than that of 7 days i.e., the 1st month after the cardiac catheterization could be better

CONCLUSION

Weight-adjusted higher dosage of UFH in TRA for diagnosis yielded remarkable results in reducing the rates of early RAO against the standard administered dosage. The beneficial results produced by the usage of high dose UFH were found to be without an increase in major bleedings. Considering that RAO affects almost 5.7% of the patients undergoing TRA, referring them a higher dosage of UFH might be a sensible choice for the prevention of RAO.

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