Efficacy of a single dose intravenous heparin in reducing sheath-thrombus formation during diagnostic angiography: A randomized controlled trial

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Background: Femoral arterial sheath thrombosis and distal embolization are well-recognized complications of cardiac catheterization but the occlusion is extremely rare. Heparinized saline flushes are used during diagnostic coronary angiography to prevent thrombus formation within the sheath lumen. However, the use of prophylactic intravenous heparin following the femoral arterial sheath insertion is controversial. The aim of this study is to evaluate the effectiveness of 2000 units of intravenous heparin bolus in comparison to a saline placebo on the thrombus formation within the arterial sheath during the diagnostic coronary angiography.

Methods: Eligible patients were randomized to receive either a study drug or placebo at the time of femoral sheath insertion. The sheath was aspirated and flushed for any presence of thrombus after each catheter exchange and at the end of the procedure. Five milliliters of blood were extracted and visualized on clean gauze followed by a saline flush. The primary end-point was the effectiveness of the study drug on reducing the incidence of sheath-thrombus formation.

Results: Three hundred and twenty patients were randomized into two arms. Three hundred and four patients were analyzed: 147 patients in heparin arm and 157 patients in placebo arm after exclusion of 13 patients in heparin arm and three in placebo arm because of incomplete reports. The baseline characteristics were similar and sheath-thrombi formation was observed in 20% of the total cohort.

Of the heparin arm, 12% (19 patients) developed sheath-thrombus formation, whereas 26% (42 patients) in the placebo arm, p-value = 0.002. An adjusted logistic regression model showed that the only predictor for the sheath-thrombus formation was the study drug (i.e. heparin). The odds ratio of developing a thrombus in the control arm was 2.5 (95% CI: 1.4–4.5, p = 0.003). There were no bleeding events observed.

Conclusion: The risk of thrombus formation is significant and intravenous heparin significantly reduced thrombus formation during diagnostic coronary angiography, with no excess bleeding events.

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Keywords: Femoral arterial access, Thrombus formation, Cardiac catheterization, Heparin
Introduction

Percutaneous cardiac catheterizations are carried out with various types of plastic catheters with variable thrombogenicity and a variety of local vascular complications. Catheter manipulations and exchanges directly through the femoral artery may cause repetitive trauma at the insertion site. Thrombosis at the puncture site has been reported in 44–54% of percutaneous cardiac catheterizations [5,15]. However, the clinical events of thrombotic vascular occlusion are less common: reports showed that clinical arterial thrombosis was diagnosed in 0.5–1% of cases [6,12]. Jacobsson and Schlossman reported femoral arterial thrombotic events in 1.4% of cases, while Siegelman et al. reported that the surgical thrombectomy was required in 2.3% of femoral angiograms made prior to withdrawal of the arterial sheath [9,14].

A heparinized saline flush is used routinely to prevent thrombus formation within the femoral sheath lumen during coronary angiography. Systemic heparinization during the catheterization procedure had been advocated to decrease the risk of thrombus formation [11]. The available data are old and no recent trial to assess this issue in the current advanced technology.

This study was conducted to evaluate the effectiveness of heparin bolus versus saline placebo on thrombus formation within arterial sheaths during the diagnostic coronary angiography.

Materials and methods

A single-center, double-blind, randomized controlled trial, evaluating the effectiveness of intravenous heparin bolus in the prevention of femoral arterial sheath-thrombus formation in patients undergoing diagnostic coronary angiography. This included all adult patients undergoing diagnostic cardiac catheterization, as well as patients with abnormal coagulation profiles, abnormal platelet counts and those receiving anticoagulation, or glycoprotein IIb/IIIa antagonists were excluded. Patients were recruited from day-cases and inpatient wards of the Prince Sultan Cardiac Center, Riyadh, Saudi Arabia.

All patients gave informed consent, and the study protocol was approved by the Institutional Ethics Committee.

After insertion of the femoral arterial sheath, each group was allocated to a concealed 2 ml solution containing either 2000 units of heparin or a saline placebo which were blinded to both patient and the operator. Arterial access was obtained via femoral approach and Super Arrow-flex 6F radiopaque polyurethane Sheaths were used. The type of sheaths and catheters used and the duration of the procedure were recorded. The femoral sheath was aspirated and flushed for any presence of thrombi after each catheter exchange and at the end of the procedure. A two-step aspiration was performed where 5 ml of blood were extracted in one syringe then another saline-filled syringe was used for flushing. Clean, white gauze was used to determine any presence of thrombi and, if thrombi were noticed, further aspiration was performed followed by a saline flush. Any thrombus of any size, as seen by the naked eye, was considered positive. The patients were evaluated and assessed clinically during their hospital stay for any presence of leg ischemia, femoral and pedal pulses, local hematoma or bleeding.

Randomization

Patients were randomized-based on catheterization laboratory flow, where the first laboratory was assigned to treatment number one and the second laboratory was assigned to treatment number two on alternate days, with sealed and labeled syringes that contained the treatment allocation, which came from pharmacy on a daily basis and were handed to an independent laboratory staff nurse assigned to maintain the concealment to patients and healthcare providers.

Outcomes

The primary end-point was the incidence of arterial sheath thrombi, defined as any visible thrombus during sheath blood aspiration at any stage of the procedure.

Patients were monitored for embolic and bleeding events until hospital discharge. Embolic events were defined as the appearance of symptoms and signs of acute limb ischemia (e.g. acute leg pain and loss of pedal pulses that result in interventional or surgical exploration). Bleeding events were defined as local femoral access bleeding or clinically detectable hematoma that leads to a drop in hemoglobin of more than 1 g/dl or blood transfusion.

The diagnosis of embolization or hematoma was made clinically (loss of arterial pulse or evidence of leg ischemia) and confirmed by Doppler studies when appropriate.

Outcomes were assessed by the patients’ treating physicians who were aware of trial assignment but still blinded for drug assignment.
Statistical analysis

A statistical software package (SAS, Version 9.2, SAS Institute, and Cary, NC) was used for all statistical analyses. Categorical data were summarized as frequencies and percentages, and continuous variables were summarized as means, medians and standard deviations (SDs). Categorical variables were compared with chi-square test and continuous variables were compared using Student’s $t$-test.

Multivariable logistic regression modeling was used to identify possible independent predictors of sheath thrombosis. All variable analysis, as well as stepwise, forward and backward modeling techniques, was used. Model calibrations and fit were assessed with Hosmer–Lemeshow goodness-of-fit statistics. A $p$-value of less than 0.05 was considered significant.

Results

Three hundred and twenty patients were randomized into two arms. Three hundred and four patients were analyzed: 147 patients in heparin arm and 157 patients in placebo arm after exclusion of 13 patients in heparin arm and three in placebo arm because of incomplete reports. The baseline characteristics of the study patients are presented in Table 1. Hypertension was observed more in the placebo group than in the treatment group (71% versus 59%, respectively; $p$-value = 0.04). Other variables were not significantly different between the two groups.

There was no significant influence of procedure duration and type of contrast used between the two groups.

Efficacy and safety of intravenous heparin bolus

There were neither bleeding nor clinically detectable hematomas observed in both groups. There were no clinical limb ischemia or femoral embolization observed in this study.

Of the patients who received heparin (19/147), 12% developed femoral sheath thrombi, com-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (N = 157), Number (%)</th>
<th>Heparin group (N=147), Number (%)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>58.2 (±10.6)</td>
<td>60.2 (±11.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Male gender</td>
<td>107 (68)</td>
<td>111 (75)</td>
<td>0.25</td>
</tr>
<tr>
<td>HTN</td>
<td>106 (71)</td>
<td>79 (59)</td>
<td>0.04</td>
</tr>
<tr>
<td>DM</td>
<td>90 (61)</td>
<td>70 (55)</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>27 (20)</td>
<td>36 (31)</td>
<td>0.03</td>
</tr>
<tr>
<td>CAD</td>
<td>98 (70)</td>
<td>77 (62)</td>
<td>0.2</td>
</tr>
<tr>
<td>Prior MI</td>
<td>37 (29)</td>
<td>47 (40)</td>
<td>0.09</td>
</tr>
<tr>
<td>CHF</td>
<td>10 (7)</td>
<td>9 (7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>146 (97)</td>
<td>138 (98)</td>
<td>0.7</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>135 (92)</td>
<td>125 (90)</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of procedure (mean ± SD)</td>
<td>14.4 (±5.9)</td>
<td>14.5 (±6.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Contrast amount (mean ± SD)</td>
<td>42.2 (±19.4)</td>
<td>41.5 (±21.8)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
pared with (42/157) 26% of the placebo arm (Fig. 1). Among those who were allocated to the heparin arm, significantly less patients in this group than in the placebo arm had a femoral thrombi during diagnostic coronary angiography.

However, there were no clinically significant ischemic or bleeding events in both groups. The femoral sheath thrombi were found in 20% (61/304) of cases, the majority occurring in the placebo arm 69% (42/61), while 31% (19/61) was found in the heparin arm. This result was independent of other factors such as anti-platelet therapy with aspirin and clopidogrel or the presence of heart failure. The odds ratio of developing a thrombus when heparin is not used was 2.5 (95% CI: 1.4–4.5, \( p = 0.003 \)); therefore, heparin administration reduced the incidence of sheath thrombi by 50% with a 14% absolute risk reduction.

Discussion

Percutaneous arterial catheterization using the Seldinger technique for various vascular catheterization procedures is the standard method of vascular puncture. Our study has shown a 20% incidence of visible thrombus formation, which is much lower than what had been reported in the past (44–54%) [5,14]. The mechanisms of thrombus formation could be related to local arterial trauma or to the thrombogenic sheath as a foreign body inside the artery enhancing the thrombus deposition. The thrombus formation was observed as early as 15 min after the introduction of the catheter [5]. The clinical events of thrombotic vascular occlusion are less common and were found in 0.5–1.4% of cases [6,9,12]. Post-cardiac catheterization femoral arterial thrombosis requiring surgical thrombectomy was reported in 0.2–2.5% [1–4,8,14]. In our data we observed femoral sheath thrombi in 20% of cases. This risk was reduced to half by the administration of intravenous heparin bolus at the time of the initial vascular access without an increase in the bleeding risk. Frequent routine aspirations and heparinized saline flushes are recommended to maintain sheath patency and prevent any risk of femoral embolization [15]. Single-dose heparinization is an effective method of reducing the sheath-thrombus formation during cardiac catheterization. Two thousand units of heparin are safe, easily administered, and has a rapid onset [8,11]. We would encourage the routine use of systemic heparinization, when not specifically contraindicated, regardless of the approach. Our report stresses the necessity of systemic heparinization to prevent arterial sheath-thrombus formation during diagnostic cardiac catheterization. Other trials have shown similar results with an initial bolus of 2000–5000 units of heparin followed by catheter flushing with heparinized saline flushes produced decreased thrombosis risk for the duration of the study, and was considered the method of choice [7,10,13]. There was no increased frequency of hemorrhagic complications.

Study limitations

Despite being a randomized study, it represents a small sample size and single-center trial. Another potential limitation is common use of anticoagulation with enoxaparin and heparin as well as glycoprotein inhibitors in acute coronary syndrome patients excluding them from the study. On the other hand, the study was inadequately powered to assess for differences in hemorrhagic complications.

Conclusion

The risk of thrombus formation is significant and use of low dose heparin is a direct, effective and safe method of preventing arterial sheath formation during diagnostic percutaneous coronary arteriography with no increase in hemorrhagic complications at this dose.

Future research

Further studies are required to confirm the prevalence of thrombus formation and its clinical impact in a large data.

Disclosures

All authors have no conflict of interests to disclose.

References