Thromboprophylaxis in orthopaedic surgery
Mulder, Marieke

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Incidence of deep venous thrombosis after arthroplasty of the shoulder
Study protocol and preliminary results of INDRA-P study

MC Struijk-Mulder¹, HB Ettema¹, CCPM Verheyen CC¹,
JJAM van Raaij², PC Rijk³, HR Büller⁴

1 Department of Orthopedic Surgery and Traumatology, Isala Klinieken, Zwolle, the Netherlands
2 Department of Orthopedic Surgery, Martini Ziekenhuis, Groningen, the Netherlands
3 Department of Orthopedic Surgery, Medisch Centrum Leeuwarden, Leeuwarden, the Netherlands
4 Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands

Study in progress
ABSTRACT

Background
A paucity of data exists on the risk of deep venous thrombosis after shoulder arthroplasty. Currently there are few level II retrospective studies regarding the incidence of symptomatic venous thromboembolism (VTE) following shoulder arthroplasty. The incidence ranges from 0.24 to 6.8%. Symptomatic deep venous thrombosis (DVT) was found in 0.09 to 5.0 %. Symptomatic 90-day pulmonary embolism (PE) rates ranged from 0.54 to 2.3%. The highest percentages reported are even higher than those following lower extremity arthroplasty. This is the first study on the incidence of asymptomatic DVT after shoulder arthroplasty without prophylaxis.

Methods and design
A prospective cohort of 100 consecutive patients who are scheduled for shoulder arthroplasty for non-traumatic indications will be included. All eligible patients will be assessed clinically for VTE and screened for DVT by bilateral complete compression ultrasonography (CCUS) of both legs and the operated arm at day 14 postoperatively. No thromboprophylaxis will be given.

Preliminary results
The first eight included patients did not show DVT nor had symptoms of pulmonary embolism.

Discussion
This study first aims to establish the incidence of asymptomatic deep venous thrombosis as detected by ultrasound. If the incidence of VTE will be substantial, a randomized controlled clinical trial comparing pharmacological thromboprophylaxis and placebo will follow, to identify risk factors for VTE patients undergoing shoulder arthroplasty and to investigate the need for thromboprophylaxis.
BACKGROUND

Early literature showed that without prophylaxis, the risk of venographically detected deep vein thrombosis (DVT) ranges from 40% to 70% following major orthopedic procedures, such as total hip and knee arthroplasty. Therefore, following lower extremity joint replacement, it is standard practice to use pharmacological thromboprophylaxis. Literature from 1980 onwards shows lower venous thromboembolism (VTE) rates, probably because of early mobilization protocols and a significant reduction in length of hospital stay. The estimated 35-day symptomatic VTE rate without thromboprophylaxis after major orthopedic surgery is currently 4.3% (2.8% DVT and 1.5% pulmonary embolism (PE)).

Shoulder arthroplasty is considered to cause less immobilization than lower extremity joint arthroplasty, but the procedure is far more extensive than uncomplicated shoulder arthroscopy. There is a genuine possibility that the incidence of thromboembolic events is substantially higher following shoulder arthroplasty vs. routine arthroscopy, which is supported by retrospective case series.

The incidence of symptomatic VTE was only investigated in level II retrospective database studies. The incidence ranges from 0.24 to 6.8%. Two studies prospectively reported incidences of asymptomatic deep venous thrombosis after shoulder arthroplasty of respectively 0 and 13%. However, both studies used pharmacological prophylaxis with aspirin in addition to mechanical thromboprophylaxis and had sample sizes of respectively 10 and 100 patients studied.

To our knowledge, this is the first study on the incidence of symptomatic VTE and asymptomatic DVT after shoulder arthroplasty without prophylaxis. There is no consensus regarding the need for perioperative pharmacological thromboprophylaxis following shoulder arthroplasty within and amongst guidelines.

PURPOSE

The aim of our study is to establish the incidence of venous thrombo-embolic complications as detected by bilateral complete compression ultrasonography after shoulder arthroplasty without thromboprophylaxis.

We hypothesize that the incidence of VTE after shoulder arthroplasty will be higher than the baseline VTE risk of medical patients; higher than the previously reported incidence of VTE after shoulder arthroscopy and lower than the incidence of VTE after major orthopedic surgery. This is the first step to determine whether routine thromboprophylaxis is warranted after shoulder arthroplasty.
METHODS AND DESIGN

This Dutch multi-center study has started at the Isala Klinieken Zwolle and will also commence soon at the Martini Ziekenhuis, Groningen and Medisch Centrum Leeuwarden. All consecutive patients aged 18 years or older, scheduled for shoulder arthroplasty will undergo complete compression ultrasonography (CCUS) of both legs and the operated arm approximately 14 days post-procedure. Clinical data including date of birth, sex, race, weight and height are recorded at entry. Patients meeting one of the following criteria are excluded from the study: fracture of proximal humerus, inability or unwillingness to give written informed consent, inability to be followed-up, ongoing treatment with anticoagulant therapy (excluding aspirin) and a history of VTE. Exclusion criteria are limited, to keep selection bias to a minimum.

Peri-operative management

Patients are operated in beach-chair position. We use a standard deltopectoral approach. All types of shoulder prosthesis are eligible: total shoulder arthroplasty, hemi-arthroplasty, resurfacing shoulder arthroplasty and reversed shoulder prosthesis. Concomitant treatments such as rotator cuff repair, and operative time will be recorded. An intra-articular drain is inserted, and removed on the first post-operative day.

Post-operative management

A shoulder immobilizer is applied for 6 weeks. On the first post-operative day, patients are instructed by a physiotherapist regarding wrist and elbow movements, to be repeated every hour. No limitations are imposed regarding ambulatory status. A pain protocol starting with paracetamol is initiated and patients are allowed to use non-steroid anti-inflammatory drugs according to their need. Physiotherapy is continued for 6 months. Routinely patients will be admitted for two days; the day of operation and the first post-operative day. No thromboprophylaxis is given; neither during hospital stay nor after discharge. Mechanical thromboprophylaxis is also not used.

Two follow-up contacts are scheduled; when CCUS will be performed (2 weeks) and after 6 weeks in the outpatient clinic. Patients will be asked if they had had any clinical signs or symptoms of VTE following the operation. The clinical signs documented are pain, tenderness, swelling or redness of the legs, dyspnea, chest pain and hemoptyis. In addition, patients are instructed to contact the hospital if one of these signs or symptoms occur prior to a follow-up contact. If clinical symptoms of VTE occur, the patient will be referred to the department of internal medicine and either CCUS, for suspected DVT or a CT angiogram, for suspected PE will be performed. If VTE is detected, nadroparin 5700 IE s.c. will be administered twice daily for at least 5 days, until adequate INR of 2,5 - 3,5 will be reached with vitamin K antagonists, according to hospital protocols.
Complete compression ultrasonography

Three experienced ultrasound technicians perform CCUS of the leg veins and operated arm veins. All of them received a supervised period of training before participating as a sonographer in this study. The ultrasound device used is a linear L9-3 MHz sonographic scanner (Philips IU22). A standardized protocol for complete compression ultrasonography is applied\textsuperscript{16} requiring an examination time of approximately 40 minutes for both legs and 20 minutes for the arm.

The criterion for the diagnosis of DVT is inability to compress the veins with the ultrasound transducer. Ultrasonography findings are recorded as normal (negative), abnormal (positive), or inadequate for interpretation if a complete vein or segment of a vein could not be visualized. A venous thrombus of the legs is classified as proximal thrombosis (with or without concomitant calf vein thrombosis), isolated calf vein thrombosis or muscle vein thrombosis. The proximal venous system of the leg is defined as the deep veins in the pelvis, the thigh, and the popliteal region cephalad to the trifurcation of the calf veins. A venous thrombosis of the operated arm is classified as a proximal thrombosis (with or without concomitant lower arm thrombosis), or lower arm thrombosis. The proximal venous system of the arm is defined as truncus brachiocephalica, subclavian vein, axillary vein and brachial vein.

Outcome measures

The primary outcome measure of the study is the combined incidence of symptomatic and asymptomatic venous thromboembolic complications after shoulder arthroplasty during the 2-week follow-up period (as diagnosed by a single postoperative complete compression ultrasound sonography, CCUS). The secondary outcome measure is the incidence of symptomatic venous thromboembolic complications and mortality after shoulder arthroplasty during the 6 weeks of postoperative follow-up. The principal safety outcome measure is the cumulative incidence of major and clinically relevant non-major bleeding events. A major bleeding event is defined as a clinically overt hemorrhage associated with a decrease in hemoglobin requiring transfusion, a bleeding event requiring re-intervention, or a haemarthrosis with joint drainage of more than 250 mL. A clinically relevant non-major bleeding event is defined as a haemarthrosis with joint drainage of 100 to 250 mL that did not require re-intervention.

Ethics

This is an observational cohort study but since an ultrasound is performed, written informed consent is requested and the study was approved by the local ethics committee of all participating hospitals.
Statistical analysis
As the expected incidence of DVT after shoulder arthroplasty is unknown, we calculated the sample size, presuming an incidence of 10%. With a sample size of 100 patients, a sufficiently narrow confidence interval will be reached with a power of 80% and a significance level of 5%. The analysis is based on intention to treat. Incidences are presented as a proportion of the studied population. 95% confidence intervals are calculated using CIA software, (BMJ books, London) using the exact method. Continuous variables are compared using Student’s t-test or, in the case of an abnormal distribution, the Mann-Whitney U test. Categorical data are compared with cross tabulation (Chi-square, Fisher’s exact test).

Study period and data dissemination
The study has started in November 2012 at the Isala Clinics, Zwolle and will soon commence at the other two hospitals. The recruitment period will be one year. Study completion includes submission to relevant national and international conferences and peer reviewed publications.

PRELIMINARY RESULTS
During the study period, 12 consecutive patients were scheduled for shoulder arthroplasty, one of which underwent bilateral shoulder arthroplasty in two separate operations. Three patients were excluded: use of anticoagulant therapy (1 patient), inability to provide informed consent (1 patient), and the anesthetists disapproval of participation of one patient with a biological heart valve replacement, who did not use anti-coagulants. One patient did not present for the ultrasonography investigation. Thus 8 patients were included and gave their consent. The mean duration of hospital stay was 3.5 days (range, 2 to 6 days). Ultimately, 8 patients (9 procedures) were included for the analysis of the primary and secondary outcome parameters. The baseline characteristics of the 8 patients (9 procedures) who completed the ultrasonography studies are listed in Table 1.

The first eight included patients did not show any DVT on extended CUS examination, which was performed approximately 17 days after the procedure (range, 14 to 22 days). All ultrasonography scans were evaluated as adequate. Also, no symptomatic VTE episodes were reported. Regarding the principal safety outcome, no major bleeding events occurred. The patients did not require transfusions, and no bleeding events requiring re-intervention were observed. Post-thrombotic syndrome was not observed in our patient group.
DISCUSSION

To our knowledge, this is the first study on the incidence of symptomatic VTE and asymptomatic DVT after shoulder arthroplasty without prophylaxis. There is no consensus regarding the need for perioperative pharmacological thromboprophylaxis following shoulder arthroplasty within and amongst guidelines. When the incidence will be substantial, a randomized controlled clinical trial comparing thromboprophylaxis

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**Table 1.** Baseline demographic and operation characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=9)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs, mean ± SD</td>
<td>68.7 ± 9.1</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>29.1 ± 3.8</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Side, n (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Right</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>-</td>
</tr>
<tr>
<td>Contraceptives, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>-</td>
</tr>
<tr>
<td>Previous use</td>
<td>1 (11)</td>
</tr>
<tr>
<td>HRT, n (%)</td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>-</td>
</tr>
<tr>
<td>Previous use</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Family history of VTE, n (%)</td>
<td></td>
</tr>
<tr>
<td>Varicosis, n (%)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Thrombophilic factors</td>
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<tr>
<td>Anesthesia, n (%)</td>
<td></td>
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<tr>
<td>Loco regional</td>
<td>1 (11)</td>
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<tr>
<td>General</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Both</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Type of prosthesis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hemi</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Total shoulder</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Reversed</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Resurfacing</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Duration of Operation (min, Mean ± SD)</td>
<td>95 ± 28</td>
</tr>
</tbody>
</table>

BMI, body mass index; HRT, hormone replacement therapy; VTE, venous thromboembolism

* n = 9 operations in 8 patients.
and placebo will follow, to determine risk factors for VTE patients undergoing shoulder arthroplasty and to investigate the need for thromboprophylaxis.

Shoulder arthroplasty is considered to cause less immobilization than lower extremity joint arthroplasty, but the procedure is far more extensive than uncomplicated shoulder arthroscopy. There is a genuine possibility that the incidence of thromboembolic events is substantially higher following shoulder arthroplasty vs. routine arthroscopy, which is supported by retrospective case series.5-9

A paucity of data exists on the risk of deep venous thrombosis after shoulder arthroplasty. Currently there are few level II retrospective studies regarding the incidence of symptomatic VTE following shoulder arthroplasty.5-9 The incidence ranges from 0.24 to 6.8 %. Symptomatic DVT was found in 0.09 to 5.0 %. Symptomatic 90-day PE rate ranged from 0.54 - 2.3%. The highest percentages reported are even higher than those following lower extremity arthroplasty.

Two studies prospectively investigated the incidence of asymptomatic deep venous thrombosis after shoulder arthroplasty. Incidences of 0 to 13% of DVT, using both aspirin and mechanical thromboprophylaxis, were detected by color-flow Doppler ultrasound.10-11 Widmer et al.10 included 10 patients who underwent hemi arthroplasty after a proximal humeral fracture and the ultrasound was performed at postoperative day 14. Willis et al.11 included 100 patients: in all patients the ultrasound was performed at postoperative day 2, and in 50 patients the ultrasound was repeated at week 12.

Likewise, no randomized controlled clinical trials on VTE after shoulder arthroscopy could be found in literature. Only four retrospective case series after shoulder arthroscopy could be found, with incidences of symptomatic VTE ranging from 0.011 to 0.38%. (DVT: 0.0046-0.38; PE: 0.008-0.26).9,12-14

**Limitations**

One potential limitation of our study is the relatively small number of patients, even if completed to 100 cases. Because of this, a risk factor analysis for the development of VTE in our population will be limited.

Secondly, ultrasonography was chosen over contrast venography to assess the incidence of deep venous thrombosis, potentially underestimating the actual incidence. Contrast venography is a more sensitive method for detecting DVT and considered to be the golden standard.2,17,18 Venography is invasive however. Up to 20% of venograms is considered inadequate for evaluation,19 a considerable degree of intra-observer and inter-observer variation is present19 and the clinical relevance of small thrombi is uncertain.20 Therefore, the use of venography as a screening test in unselected patients is undesirable. Ultrasound is non-invasive, and repeatable. The accuracy of ultrasound is somewhat reduced for the calf veins however, and it is operator dependent.19
and specificity for the detection of symptomatic DVT with ultrasound is equivalent to venography. However, combined data from 11 level 1 studies investigating the utility of various US techniques for the diagnosis of asymptomatic DVT in orthopedic patients demonstrated a sensitivity of 62% for proximal and 48% for below-knee DVTs. Reduced sensitivity can be explained by the fact that asymptomatic thrombi are more likely to be fresh, smaller and non-occlusive than their symptomatic counterparts.

The presence of pre-operative asymptomatic thrombi will not be determined in this study. However, a low baseline risk in this patient group without prior history of VTE can be assumed. Furthermore we will exclude patients with a history of VTE potentially causing a further underestimation of the risk of VTE.

Finally, results from prospective cohort studies have shown that most asymptomatic thrombi in patients undergoing hip or knee replacement remain clinically silent. These results raise questions about the clinical relevance of asymptomatic DVT detected by ultrasound. There is, however, a relation between asymptomatic DVT and symptomatic VTE. It remains unclear which percentage of asymptomatic lower leg thrombi propagates proximally from where they might cause pulmonary embolism. (In symptomatic calf vein clots, 20% propagate proximally and asymptomatic proximal DVTs have demonstrated a risk of symptomatic PE in 40%). Both phenomena (VTE/DVT) are symptoms of the same disease process of hypercoagulability, a condition we believe should be prevented.
REFERENCES


