Pocket related Complications in 164 Patients receiving Anticoagulation or dual Antiplatelet therapy undergoing Heart Rhythm Device Implantation: D-Stat™ Flowable Hemostat versus vacuum drainage

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COI

• None of the authors have any conflict of interest to declare
Introduction

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  – undergoing pacemaker or ICD implantation either for primary/secondary prevention or cardiac resynchronisation
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  – receiving combination of aspirin and clopidogrel to prevent thrombosis after stent implantation

• In a series of >3,000 pt undergoing ICD or pacemaker implantation, 40% and 33% received anticoagulation or antiplatelet therapy (1)

Introduction

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(1) Udo E et al. Heart Rhythm 2012;9:728
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- In patients receiving anticoagulation or antiplatelet therapy, the rate of pocket related complications increases up to 25% (2).
- Pocket related complications prolong the hospital stay by an average of 3.1 (1-10) days (3)
- The additional cost of treating a hematoma/hemorrhage is $6,995 (3)

(3) Reynolds M et al. J Am Coll Cardiol 2006;47:2493-97
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  – Previous studies report on different immunogenetic potential of various collagen implants, demonstrating increased antibody titers against collagen in vivo in some of them. In an experimental rat bone defect model, histological differences in the healing process were observed between different hemostats.

Introduction

D-Stat™ Flowable Hemostat

5000 IU thrombin, 200 mg collagen, diluents, and mixing accessories.
Objective

to evaluate the

• Primary endpoint
  – Composite of hematoma needing evacuation and pocket infection

• Secondary endpoints
  – effectiveness (reduction of hematoma formation) and
  – safety (pocket infection; antigenicity, immunogenicity and inflammation)

associated with the use of D-Stat™ Flowable Hemostat compared to vacuum drainage system following implantation of cardiac pacemakers, implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy (CRT) in patients receiving anticoagulation or dual platelet inhibition
Methods

• prospective single center randomized study

• Inclusion criteria:
  – Need for first permanent pacemaker, ICD, or CRT/D implantation
  – Receiving anticoagulation and/or dual platelet inhibition.

• Exclusion criteria:
  – Known allergy against bovine collagen
  – Need for submuscular implantation of the device
Methods

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• In patients receiving weight adjusted low molecular weight heparin (LMWH), this medication was terminated 12 h before the operation and restarted 12 h after surgery.
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• In patients receiving weight adjusted low molecular weight heparin (LMWH), this medication was terminated 12 h before the operation and restarted 12 h after surgery.

• Oral anticoagulation treatment or dual platelet inhibition was continued. For patients receiving oral anticoagulation, an international normalized ratio (INR) of ≥1.8 and <3.0 was required
Methods

• Operative approach
  – Pectoral incision after administration of antibiotics and local anesthesia
  – Venous access achieved by puncture of the subclavian vein
  – Atrial leads with active fixation
  – Ventricular leads with passive fixation, except in cases of severe tricuspid regurgitation or pulmonary hypertension
  – Hemostasis was achieved by using standard of care (compression, electrocautery)
  – D-Stat™ Flowable Hemostat was applied into the pocket prior lead connection and insertion of the generator or
  – Vacuum drainage insertion
  – All devices were placed in a subcutaneous/subfascial pocket.
  – After the procedure, a pressure dressing was applied for 24 h in combination with bed rest
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  – All devices were placed in a subcutaneous pocket.
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• 24 h post device implantation C-reactive protein and Immunoglobulin E were measured

• Patients were examined daily until hospital discharge and thereafter in larger intervals in the outpatient clinic
Methods

• Definitions
  – **Minor pocket hematoma**: palpable mass that protruded >2 cm
  – **significant pocket hematoma**: palpable mass that protruded >4 cm
  – **Pocket hematomas requiring operative evacuation**: tense swelling with poor capillary perfusion, progressive enlargement, or severe pain to the patient
  – The incidence of early skin erosions or pocket **infections** within the first 3 months after implantation was assessed
Results

• During one year 164 out of 484 (33.9%) consecutive patients matched the inclusion criteria and were included in the study.
• Mean INR at the time of implant was 2.1 ± 0.3 (D-Stat group) versus 2.1 ± 0.5 (control group) (p=0.82), ranging from 1.8 to 2.8.
• Follow-up (2.8±1.8 months) was complete in all patients
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>D-Stat group</th>
<th>Drainage group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years]</strong></td>
<td>73±11</td>
<td>73±10.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Female gender [n (%)]</td>
<td>22 (27)</td>
<td>24 (29)</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>28±4</td>
<td>27±6</td>
<td>0.5</td>
</tr>
<tr>
<td>Atrial fibrillation [n (%)]</td>
<td>49 (60)</td>
<td>45 (55)</td>
<td>0.6</td>
</tr>
<tr>
<td>Artificial aortic or mitral valve [n (%)]</td>
<td>5 (6)</td>
<td>5 (6)</td>
<td>1</td>
</tr>
<tr>
<td>Recent implantation of a coronary stent [n (%)]</td>
<td>31 (38)</td>
<td>39 (48)</td>
<td>0.2</td>
</tr>
<tr>
<td>Recent implantation of a percutaneous valve [n (%)]</td>
<td>4 (5)</td>
<td>2 (2)</td>
<td>0.4</td>
</tr>
<tr>
<td>ICD/CRT-D [n (%)]</td>
<td>53 (65)</td>
<td>45 (55)</td>
<td>0.3</td>
</tr>
<tr>
<td>Anticoagulation [n (%)]</td>
<td>47 (57)</td>
<td>36 (44)</td>
<td>0.1</td>
</tr>
<tr>
<td>Coumadin therapy</td>
<td>23 (28)</td>
<td>20 (24)</td>
<td>0.7</td>
</tr>
<tr>
<td>Subcutaneous LWMH</td>
<td>13 (16)</td>
<td>9 (11)</td>
<td>0.8</td>
</tr>
<tr>
<td>Intravenous UFH</td>
<td>11 (13)</td>
<td>7 (9)</td>
<td>0.8</td>
</tr>
<tr>
<td>Dual antiplatelet therapy [n (%)]</td>
<td>28 (34)</td>
<td>41 (50)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Anticoagulation + DAPT [n (%)]</td>
<td>7 (9)</td>
<td>4 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Coumadin therapy + DAPT</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Subcutaneous LWMH + DAPT</td>
<td>2 (2)</td>
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<td>Intravenous UFH + DAPT</td>
<td>2 (2)</td>
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</tr>
</tbody>
</table>
Results

• Primary endpoint:
  – 12/82 patients of the D-Stat group had a significantly increased incidence of the combined endpoint (hematoma needing operative evacuation and pocket infection) during follow-up compared to 0/82 of the drainage group (14.6% versus 0%; p<0.01).
Results

• Effectiveness endpoint: Incidence of hematoma after device implantation

  – Pocket hematoma occurred in 17/82 (20.7%) and in 16/82 (19.5%) patients of the D-Stat and control groups, respectively (p=1.0), and occurred in all patients in both groups at pre-discharge
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  – Pocket hematoma occurred in 17/82 (20.7%) and in 15/77 (19.5%) patients of the D-Stat and control groups, respectively (p=1.0), and occurred in all patients in both groups at pre-discharge

  – 7/82 (8.5%) and 0/82 (0%) patients of the D-Stat and control group, respectively, required operative evacuation (p=0.01), with no need for blood transfusion
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  - 7/82 (8.5%) and 0/82 (0%) patients of the D-Stat and control group, respectively, required operative evacuation (p=0.01), with no need for blood transfusion.

  - Also no benefit in the highest risk group for pocket hematoma formation (patients receiving dual platelet inhibition plus anticoagulation “triple therapy”) (8.7% versus 5%; p=0.4).
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  – 7/82 (8.5%) and 0/82 (0%) patients of the D-Stat and control group, respectively, required operative evacuation (p=0.01), with no need for blood transfusion
  – Also no benefit in the highest risk group for pocket hematoma formation (patients receiving dual platelet inhibition plus anticoagulation “triple therapy”) (8.7% versus 12.4%; p=0.46).
Results

Safety endpoints:

1. Incidence of infection after device implantation
   – Pocket infection developed in 5/82 (6.1%) and in 0/82 (0%) patients of the D-Stat and control group, respectively (p=0.06).
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1. Incidence of infection after device implantation
   - Pocket infection developed in 5/82 (6.1%) and in 0/82 (0%) patients of the D-Stat and control group, respectively (p=0.06).
   - One patient with a pocket infection in the D-Stat group (1.2%) died in septic shock despite of early removal of the ICD system
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   - One patient with a pocket infection in the D-Stat group (1.2%) died in septic shock despite of early removal of the ICD system.

2. Antigenicity, immunogenicity and inflammation
   - Postoperative Immunoglobulin E levels and postoperative increase of C-reactive protein were similar in both groups (p=0.26 and p=0.4, respectively).
Discussion

Efficacy of hemostat

- The results of our study suggest that the administration of D-Stat™ Flowable Hemostat does not decrease the incidence of clinical relevant hematoma compared to vacuum drainage
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• The results of our study suggest that the administration of D-Stat™ Flowable Hemostat does not decrease the incidence of clinical relevant hematoma compared to vacuum drainage.

• In the Slotwiner¹ study, the benefit of D-Stat was found solely in patients receiving pacemakers whereas patients undergoing ICD implantation did not benefit. The majority of patients in our series underwent ICD device implantation.

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- For patients receiving coumadin therapy, a preoperative INR of less than 2.0 was required in their study. In contrast, patients in our series were at higher risk for bleeding complications and underwent device implantation if the INR was ≥1.8 and 3.0.
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• Furthermore, 7% of our patients received triple therapy (dual platelet inhibition plus anticoagulation).
Discussion

Pocket infection and local haemostat use

• We observed in our series a markedly increased rate of pocket infections in the D-Stat group compared to controls (6.1% versus 0%) during the follow-up period of ~3 months.
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• We observed in our series a markedly increased rate of pocket infections in the D-Stat group compared to controls (6.1% versus 0%) during the follow-up period of ~3 months.

• Although this increase was not statistically significant (p=0.06), the use of D-Stat Flowable was prematurely stopped by our institutional clinical event committee during a planned interim analysis.
Discussion
Pocket infection and local haemostat use

• We observed in our series a markedly increased rate of pocket infections in the D-Stat group compared to controls (4.9% versus 1.3%) during the follow-up period of 3.7 month.

• Although this increase was not statistically significant, the use of D-Stat Flowable was prematurely stopped by our institutional clinical event committee during a planned interim analysis.

• The reason for this observation is unclear,

• previous studies reported no infectious complications, or only report on ”pocket related complications” in general without providing results for infectious complications.
Discussion

• However, hemostats are known to enhance the risk of infection at the application site and have been reported to potentiate bacterial growth. Even a small amount of local haemostat enhanced especially anaerobic infection, and a comment related to this problem is included in the D-Stat instructions for use stating that “hemostatic agents may serve as a nidus for infection and abscess formation”.

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• Whether addition of antibiotics to hemostats in order to provide local antimicrobial effect during tissue healing will solve this problem is also not known. Addition of antibiotics to one of the components of hemostats has demonstrated a significant reduction of postoperative infectious complications in early studies.
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Antigenicity, immunogenicity and inflammation after local haemostat use

• The markers of antigenicity, immunogenicity and inflammation chosen in our study were not different in the D-Stat group and control group. This might serve as a marker of low immunoglobulin E - mediated antigenic, immunogenic, and inflammatoric properties of D-Stat flowable
Thank you
## Results

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<thead>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>17 (20.7)</td>
<td>16 (19.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pocket hematoma requiring evacuation</td>
<td>7 (8.5)</td>
<td>0 (0.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Significant pocket hematoma</td>
<td>7 (8.5)</td>
<td>5 (6.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Minor pocket hematoma</td>
<td>3 (3.7)</td>
<td>11 (13.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>5 (6.1)</td>
<td>0 (0.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>3 (3.7)</td>
<td>3 (3.7)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>1</td>
</tr>
</tbody>
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