Workshop Clinici Interattivi (2)
Distorsioni e piccoli traumi agli arti inferiori: dobbiamo prescrivere eparine proprio a tutti?

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Scenario Clinico (1)

• La signora Anna, impiegata di 33 anni da sempre in buona salute, mi chiama per una visita domiciliare perché, in seguito a distorsione non complicata della caviglia, in P.S. le hanno prescritto 15 giorni di gambaletto gessato ed eparina a basso peso molecolare (LMWH) per 20 giorni.

• Circa un anno prima, per analoga distorsione, in altro ospedale le avevano consigliato solo fasciatura stretta per 10 giorni, senza prescrizione di sostanze eparino-simile.

Scenario Clinico (2)

• Sollecitato dalla perplessità della paziente sulla necessità delle prescrizioni, condivido l’immobilizzazione della caviglia, ma ho qualche perplessità sulla prescrizione di LMWH.

CLINICAL QUESTIONS

A. Quanto stimi il rischio di complicanze tromboemboliche (TVP, EP) in una donna sana di 33 anni con distorsione della caviglia?
1. Nessuno
2. Basso
3. Medio
4. Elevato
5. Molto elevato

Profilassi della Malattia tromboembolica Linee guida

• SIGN, 2002
• American College of Chest Physicians, 2001
Although DVT appears to occur with moderate frequency after isolated lower extremity fractures, there are few prospective studies available, and none have reported the incidence of clinically important VTE.

Routine administration of LMWH in these patients cannot currently be recommended because of uncertainty about whether the benefits of prophylaxis outweigh the risks and whether prophylaxis is cost-effective.

Clearly, more research is required in this area.

La linea guida prodotta dal SIGN non riporta alcuna sezione sui traumi della caviglia.
Table 1: Risk factors for venous thromboembolism

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMOBILITY</td>
<td>Bedrest &gt;3 days</td>
<td>10 x risk (increases with duration)</td>
</tr>
<tr>
<td></td>
<td>Plaster cast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paralysis</td>
<td></td>
</tr>
</tbody>
</table>

Triggers risk factors associated with DVT included:
- application of a plaster cast to the lower extremities (OR 36.47)
- orthopedic surgery (OR 16.25)
- general surgery (OR 9.46)

Samama MM. Arch Intern Med, 2000

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Samama MM.

An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study

Arch Intern Med 2000;160:3415-20
C. Ritieni appropriata nella sig.ra Anna la prescrizione di eparine a basso peso molecolare?
1. Sì
2. No

Note ed EBM
Alcune riflessioni sull’appropriatezza nell’uso dei farmaci

- Un trattamento è appropriato se:
  - è di efficacia provata
  - la prescrizione riguarda indicazioni cliniche per le quali è stata dimostrata l’efficacia
  - gli effetti sfavorevoli sono “accettabili” rispetto ai vantaggi terapeutici

Il rischio basale

“Trattare i pazienti a basso rischio è una strategia molto rischiosa perché il vantaggio che il singolo individuo può ottenere da un programma di prevenzione può essere annullato dal rischio - anche minimo - che implica lo stesso intervento preventivo.

Rose G. Int J Epidemiol 1985

Il rischio basale

- Il beneficio che il paziente individuale può ottenere da un intervento terapeutico cresce proporzionalmente al rischio basale di sviluppare un evento sfavorevole.
- Il rischio di eventi avversi conseguenti al trattamento é indipendente dal rischio basale del paziente.


Table 1 - Criteria for Inclusion of Studies

- Patients identified as belonging to the group of interest and controls equal in relevant patient characteristics
- Utmost information
  1. Observational studies: contrast-angiography only (digital or unsubtracted)
  2. Randomized studies: contrast-angiography or HLMs for leg scanners
- Randomized, at least 50 patients per group
- Comparison objectively determined and not subject to bias
- [Assessment criteria: adequate randomization, adequate information to assess quality of study]

I. Baseline Risks: Threshold
- Design: studies prospective cohort studies or control group of unadjusted risks
- Interventions: not predetermined


ACCP 2001
Two RCTs have shown that outpatient LMWH reduced the incidence of asymptomatic DVT in patients with plaster cast immobilisation.

**BACKGROUND**

Deep-vein thrombosis is a well-recognized complication after trauma to the legs and subsequent immobilization, but there are no generally accepted approaches to preventing this complication.

**METHODS**

- Double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous reviparin (1750 anti-Xa units given once daily) in 440 patients who required immobilization in a plaster cast or brace for at least five weeks after a leg fracture or rupture of the Achilles tendon.
- The study drug was given during the period of immobilization.
-Venography of the injured leg was performed within one week after removal of the plaster cast or brace, or earlier if there were symptoms suggesting deep-vein thrombosis.

**RESULTS**

- Deep-vein thrombosis was diagnosed in 17 of the 183 patients (9%) assigned to receive reviparin and in 35 of the 188 patients assigned to receive placebo (19%).
- Most of the thromboses were distal (14 in the reviparin group and 25 in the placebo group).
- There were no differences between the two groups with respect to bleeding or other adverse events.

**RCTs di prevenzione con LMWH**

CONCLUSIONS

• Deep-vein thrombosis is common in persons with leg injury requiring prolonged immobilization.
• Reviparin given once daily appears to be effective and safe in reducing the risk of this complication.

Our study suggests that the routine use of reviparin for prophylaxis against thrombosis during the period of leg immobilization after fracture of the leg or rupture of the Achilles tendon is beneficial.

However, further evaluation is warranted before such treatment can be recommended for routine use.

It will be important to determine whether this therapy can reduce the risk of long-term sequelae of deep-vein thrombosis, such as venous insufficiency, and to assess its cost effectiveness.

Table 2. Risk of Thromboembolic Events Within One Week after Removal of a Plaster Cast or Brace Among Patients Randomly Assigned to Treatment with Reviparin or Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Reviparin</th>
<th>Placebo</th>
<th>Odds Ratio 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blonde.</td>
<td>n=131 (4)</td>
<td>n=158 (5)</td>
<td>0.75 (0.49-1.18)</td>
<td>0.21</td>
</tr>
<tr>
<td>In the proximal segment</td>
<td>16/131 (12)</td>
<td>18/158 (11)</td>
<td>0.99 (0.59-1.60)</td>
<td>0.90</td>
</tr>
<tr>
<td>In the distal segment</td>
<td>11/131 (8)</td>
<td>25/158 (16)</td>
<td>0.11 (0.07-0.17)</td>
<td>0.09</td>
</tr>
<tr>
<td>Total</td>
<td>6/237</td>
<td>2/224 (11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number Needed to Treat (NNT)

Quanti pazienti bisogna trattare per prevenire un episodio di trombosi venosa profonda?

| Tutte le TVP* | 11 (6-43) |
| TVP prossimali | 27 (14-4667) |
| TVP distali | 18 (16-1291) |

* Con l’analisi per intention to treat NNT=12 (7-50)

Conflict of interest in medical research

• The authors designed the study, interpreted the data, and wrote the article.
• All the data were collected by a Danish contract research organization and transferred to the statistical department of the sponsor, Knoll.
• The authors had full access to the data and reviewed the statistical plan and analyses.
• The final statistical analysis was performed by the sponsor.
• The central adjudication committee was independent of the sponsor.
Conflict of interest in medical research

Supported by a grant from Knoll, Knoll provided the revaparin that was treated in the study.

Dr. Lassen and Morris have served as consultants to Knoll and other companies that develop antithrombotic compounds. Dr. Nutt is an employee of Knoll.

We are indebted to Silke Warniqner of Knoll for contributions to the statistical analysis.


2. Distorsioni e piccoli traumi agli arti inferiori: dobbiamo prescrivere eparine proprio a tutti?

D. Le eparine a basso peso molecolare possono causare piastrinopenia?

1. Sì
2. No

• Clinically important heparin induced thrombocytopenia (HIT) is immune mediated and usually occurs between five and 10 days (up to 20 days) after initiation of heparin.

• It can occur at any dose of either UFH or LMWH.

• LMWH is less likely than UFH to be associated with antiplatelet antibodies.

• HAT should be considered in any patient whose platelet count falls by 50% or more.

College of American Pathologists
Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia
Arch Pathol Lab Med 2002;126:1415–1423

• An unusual aspect of HIT is its variable frequency, depending on the type of heparin

• Unfractionated heparin (UFH) is more likely to cause both HIT antibody formation and clinical HIT, compared with low-molecular-weight heparin (LMWH).

E. Ritieni necessario, nella sig.ra Anna, monitorare il trattamento eparinico con indagini di laboratorio?

1. No
2. Conta piastrinica
3. PTT
4. Conta piastrinica + PTT
Administration, dosage and coagulation monitoring

• In general, monitoring of the anticoagulant effect of low dose UFH or LMWH is not required.

• As LMWHs have little effect on the APTT, plasma anti-Xa activity should be measured instead:
  - in in high-risk pregnancy
  - if there are complications such as haemorrhage or accidental overdose
  - in patients with renal failure given higher doses of LMWH

Platelet Count Monitoring

• The frequency of platelet count monitoring should take into account the risk for HIT, which depends on the type of heparin used and the patient population

• Medical and obstetrical patients receiving prophylactic or therapeutic doses of LMWH have a low risk of HIT (probably less than 0.2%), and many physicians would not perform routine platelet count monitoring.

Table 4. Recommendations: Platelet Count Monitoring for Early Detection of Heparin-Induced Thrombocytopenia (HIT)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients at highest risk for HIT (postoperative patients receiving prophylactic or therapeutic dose unfractionated heparin) monitored during heparin therapy, every second day from day 4 to day 10.(^{\text{<strong>\text{</strong>}}}) Level 1</td>
</tr>
<tr>
<td>2</td>
<td>Patients at intermediate risk for HIT (medical or obstetrical patients receiving prophylactic or therapeutic dose unfractionated heparin, patients presenting renal insufficiency, patients receiving prophylactic dose low molecular weight heparin, or patients receiving unfractionated heparin with anticoagulation therapy, monitored during heparin therapy, 2 or 3 times from day 4 to day 10.(^{\text{<strong>\text{</strong>}}}) Level 2</td>
</tr>
<tr>
<td>3</td>
<td>Patients at low risk for HIT (medical or obstetrical patients receiving prophylactic or therapeutic dose low molecular weight heparin, medical patients receiving anticoagulation therapy with unfractionated heparin) routine monitoring is not recommended.(^{\text{<strong>\text{</strong>}}}) Level 3</td>
</tr>
</tbody>
</table>

Boneu B, de Moerloose P.

How and when to monitor a patient treated with low molecular weight heparin

Semin Thromb Hemost 2001;27:519-22

• Curative (but not prophylactic) administration of PMWH should be monitored with an anti–factor Xa assay in patients presenting renal insufficiency, in the elderly, and in patients presenting an increased hemorrhagic risk.

Scenario Clinico (3)

• Malgrado non condividessi la prescrizione di LMWH fatta in PS, “per stare tranquillo” ho ritenuto di trascriverla.

• Non ho ritenuto necessario eseguire alcun esame di laboratorio per il monitoraggio del trattamento.