Lepirudin treatment in a boy with suspected HIT II after surgery because of tetralogy of Fallot

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Summary
Heparin-induced thrombocytopenia (HIT II) in childhood is rare. Suspected HIT II requires immediate diagnostic and therapeutic measures in order to avoid potentially life threatening complications. Heparin must be stopped immediately.

We report on a 6-year old boy who required cardiac surgery due to tetralogy of Fallot. To our knowledge he had been exposed to heparin for the first time during cardiac catheterization on the day before surgery. Preoperatively, platelet count was normal. Postoperatively (3 days after heparin exposure), he developed pulmonary and renal failure and required inotropic cardiac support and dialysis. He also developed progressive (severe) thrombocytopenia under heparin therapy on day 2–3 postoperatively. The dialysis filter required daily exchanges due to clotting despite increasing heparin doses. The first ELISA for HIT on postop day 4 was negative. 3 days later a repeated test was positive. Von Willebrand factor antigen and D-dimers were markedly increased. The patient was immediately switched to lepirudin and subsequently stabilized slowly. No major systemic thrombosis occurred. After lepirudin treatment for 6 weeks the patient was fully recovered and HIT II-testing was negative again. Conclusion: In children with progressive thrombocytopenia in the setting of heparin exposure and signs of major or micro thrombosis HIT II must be ruled out. Even if a first early test turns out negative repeated testing should be performed. Lepirudin anticoagulation is effective and should be monitored correctly. Platelet transfusion should be avoided in HIT II.

Schlüsselwörter
HIT, Kind, Lepirudin, Herzchirurgie, Nierenversagen, Thrombozytopenie

Zusammenfassung
Die Heparin-induzierte Thrombozytopenie (HIT II) ist im Kindesalter selten. Die Verdachtsdiagnose erfordert sofortige diagnostische und therapeutische Maßnahmen, um lebensbedrohliche Komplikationen zu vermeiden.

Keywords
HIT, child, lepirudin, cardiac surgery, renal failure, thrombocytopenia

Unfractionated heparin (UFH) is used for prophylaxis and therapy of thrombotic events in children. Heparin induced thrombocytopenia type II (HIT II) is the most serious complication. The underlying pathomechanism is complex; it includes an antibody formation against heparin and platelet factor 4 (PF-4) (7). Usually, HIT II occurs after 5–10 days of heparin treatment. However, a more rapid onset can occur, especially when heparin had been administered before (6). The frequency of HIT II amongst adults treated with UFH is up to 5%.

HIT II in children
HIT II in the paediatric population was traditionally regarded as an extreme rare event. However, during the preceeding years several authors report a significant number of cases amongst children with an estimated incidence of 1–2% (2). Paediatric intensive care patients

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are at high risk, as are patients being re-exposed to heparin (6). The higher likelihood for the use of UFH and preformed antibodies after initial exposure can explain this finding.

The diagnosis of HIT II remains difficult and the implications are immense. Clinical symptoms vary widely and isolated proof of antibodies against heparin-PF-4-complex in exposed patients is common. Thus, the criteria for the diagnosis of HIT II remain challenging. The treatment of HIT II includes immediate withdrawal of heparin and alternative anticoagulation for prevention and treatment of HIT II-related thrombosis. Different agents are in use (5) even though treatment monitoring and duration of therapy have not been standardized yet.

A boy with HIT II

We report on a case of HIT II with focus on pitfalls successful therapeutic monitoring. The boy (age: six years) was admitted for cardiac surgical intervention of tetralogy of Fallot. He had had no known heparin exposure before, but details of the medical history were not available since he came from a third world country. His preoperative platelet count was within the reference range.

UFH was first administered for cardiac catheterization the day before surgery. Operation with heart-lung-support was uneventful. He was then extubated 12 h postoperatively and heparin therapy continued. On the second postoperative day he developed pulmonary oedema, hypotension and renal failure requiring re-intubation and multi-inotropic therapy with catecholamines. Platelets were around $100 \times 10^9/l$ postoperatively and dropped to $23 \times 10^9/l$ during clinical deterioration. Thrombocytopenia was progressive despite several platelet transfusions (Fig. 1a).

On day 2 p.o. continuous renal replacement therapy (CRRT) was started. Only low-dose heparin (8 IE/kg body weight per hour) was used due to blood-stained tracheal secretions. Dialysis filter had to be replaced on a daily basis because of clotting. Therefore, heparin was gradually increased up to 30 IE/kg body weight per hour in order to keep partial thrombin time in the range of 50–70 s.

An ELISA-test for heparin-induced antibodies on day 4 p.o. was negative. The test was repeated on day 7 p.o. and turned out positive (Tab. 1). Platelet aggregation testing showed that the platelets were severely activated. Von Willebrand factor was significantly increased to 432% (normal <160%), as were D-dimers (5.6 mg/l, normal <0.5 mg/l). Heparin was stopped immediately and anticoagulation for CRRT switched to calcium-citrate. Systemic anticoagulation was changed to lepirudin (initial dose $5.5 \mu g/kg/h$). Target lepirudin levels measured by ecarin-clotting-time were 0.1–0.2 μg/ml. Lepirudin dosage was gradually increased, the maximum dose being $46 \mu g/kg/h$ after renal improvement and discontinuation of CRRT on day 20 p.o. After withstand from further platelet transfusions platelet count remained 10–20 $\times 10^9/l$ and no major bleeding occurred (Fig. 1b).

Tab. 1 Test results during the clinical course:

<table>
<thead>
<tr>
<th>testing</th>
<th>postoperative</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>day 4</td>
</tr>
<tr>
<td>ELISA for heparin-PF4</td>
<td>-</td>
</tr>
<tr>
<td>antibodies</td>
<td></td>
</tr>
<tr>
<td>heparin induced platelet</td>
<td>n/a</td>
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<tr>
<td>aggregation</td>
<td></td>
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<tr>
<td>donor platelet aggregation</td>
<td>n/a</td>
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negative and platelets did not show activation (Tab. 1). Thus, lepirudin was discontinued and the boy could be discharged one week later in complete recovery.

Discussion

This case highlights some of the difficulties associated with the diagnosis and treatment HIT II. No major systemic thrombosis occurred during the clinical course of this patient. However, secondary pulmonary deterioration and sudden renal failure were probably sequelae of small vessel occlusion due to endothelial damage. In addition, the dialysis filter had to be replaced on a daily basis because of severe clotting problems. Testing in our patient revealed pronounced elevation of von Willebrand factor antigen (VWF:Ag). Endothelial damage and platelet activation have been found to be a major component in the pathophysiology of HIT II and therefore, VWF:Ag may be used to monitor the endothelial damage (1).

Multifocal clotting led to a severe decrease in platelet count starting with clinical deterioration two days after surgery. The drop in platelet count is the name-bearing hallmark of HIT. The decrease below 100 × 10^9/L has often been regarded as diagnostic marker to differentiate between HIT types I and II. However, a higher platelet count does not exclude HIT II (6).

Regarding the postulated mechanism for thrombocytopenia in HIT II substitution of platelets will not only be of little effect but might cause aggravation of the thrombotic process as seen in the presented patient after platelet transfusion on day 19. If sustaining from platelet transfusions low platelet counts are a challenge in operated and intubated patients. No major bleeding occurred in our patient despite low platelet counts.

A first ELISA for antibodies against heparin-PF-4-complex on day 4 p. o. was negative, although clinical evidence was already suggestive. Only a second test later in the course (on day 7 p. o.) confirmed the diagnosis and caused therapeutic consequences. A positive ELISA test without further clinical manifestations of HIT II is common, especially after cardiac surgery (4). The clinical manifestations in this case were lung and renal failure and recurrent clotting of the dialysis filter. The HIPA-test was not specific because the platelets were already activated without substitution of heparin. Therefore, the diagnosis of HIT II could not be completely confirmed. However, according to the clinical improvement and the course of the platelet parameters HIT II was highly suspected.

Interestingly, D-dimers first peaked at the day of the second and positive ELISA test for HIT II and subsequently fell slowly as the patient recovered. D-dimers peaked again when a catheter-related thrombosis occurred after platelet transfusion. Hence D-dimers can be an adjunctive test to determine the therapeutic success in the course of HIT II treatment.

Anticoagulation with recombinant lepirudin (r-lepirudin) has been documented as being safe in HIT II and worked well in this case (3, 8). Therapy should be monitored closely by ecarin clotting time as the required dosage can vary significantly depending on renal function. Duration of therapy for HIT II is difficult to determine. We used clinical improvement, decrease of D-dimer level and a negative testing panel for HIT in this case. Although full recovery could be achieved, this cannot be taken as granted considering mortality has been reported to be as high as 15% (6).

Conclusion

The described case of HIT II in a 6-year old boy after cardiac surgery highlights important aspects of diagnosis and management. Diagnosis should be taken into account in the setting of:

- heparin treatment,
- thrombocytopenia,
- lung and renal failure and
- recurrent clotting of the dialysis filter.

In case of negative results the test should be repeated if clinical suspicion remains high. Function tests like HIPA (heparin induced platelet aggregation) should be performed. Heparin must be stopped immediately. Von Willebrand factor and D-dimers are markers for endothelial damage and activated coagulation respectively and may help to monitor the therapeutic course. Lepirudin dosage needs monitoring as the required dose can vary significantly depending on renal function. Platelet transfusion should be avoided after the diagnosis of HIT II has been established.

References