Monitoring of coagulation using viscoelastometry for the management of bleeding: Value, algorithms and new developments

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Disclosure of commercial interest:

Andreas Calatzis is a co-inventor of the ROTEM and Multiplate analyzers, and co-owner of the manufacturer of the ClotPro device. Received honoraria from: Roche

**United States Patent**

Calatzis et al.

[54] APPARATUS FOR MEASURING THE COAGULATION CHARACTERISTICS OF TEST LIQUIDS

[19]

**United States Patent**

Calatzis et al.

CARTRIDGE DEVICE FOR BLOOD ANALYSIS

ROTEM® is a product of Werfen / Instrumentation Laboratory / TEM

TEG® is a product of Haemonetics

Quantra is a product of Hemosonics / Stago
Acute bleeding during surgery

- enhances transfusion requirements
  - costs
  - risk of infection
  - other risks

- prolongs surgery
  - enhances costs
  - prolongs anesthesia
  - impairs outcome

- causes surgical reexplorations
  - prolongs ICU stay
  - enhances costs
  - limits outcome

- makes the surgery more difficult
  - poor visibility of the surgical field
Major Bleeding, Transfusions, and Anemia: The Deadly Triad of Cardiac Surgery

Marco Ranucci, MD, FESC, Ekaterina Baryshnikova, BD, Serenella Castelvecchio, MD, FESC, and Gabriele Pelissero, MD, PhD; for the Surgical and Clinical Outcome Research (SCORE) Group

Departments of Cardiothoracic, and Vascular Anesthesia and Intensive Care, Scientific Directorate, IRCCS Policlinico San Donato, Milan, Italy

Retrospective monocentric study
2002 – 2012
n = 16,154 consecutive patients

Studied association
„anemia“ / „bleeding“ / „transfusion“

with

Clinical complications
30d mortality

"Major bleeding is a partially modifiable risk factor, and adequate preemptive and treatment strategies should be applied to limit this event."

Table 2. Outcome in Patients With and Without Major Bleeding

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>No Major Bleeding (n = 14,325)</th>
<th>Major Bleeding (n = 1,829)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative mortality</td>
<td>370 (2.6)</td>
<td>234 (12.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red cells</td>
<td>5,657 (39.5)</td>
<td>1,438 (78.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>1,395 (9.7)</td>
<td>926 (50.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>488 (3.4)</td>
<td>402 (22.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intensive care unit length of stay (d)</td>
<td>3.0 (4.7)</td>
<td>5.5 (8.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intraaortic balloon pump</td>
<td>323 (2.3)</td>
<td>138 (7.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>73 (0.5)</td>
<td>18 (1.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>202 (1.4)</td>
<td>61 (3.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mesenteric infarction</td>
<td>26 (0.2)</td>
<td>9 (0.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>539 (3.8)</td>
<td>238 (13.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>15 (0.1)</td>
<td>8 (0.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sepsis</td>
<td>268 (1.9)</td>
<td>84 (4.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

> Bleeding: therapeutic options

- Plasma: 200 EUR for 2 units
- Platelets: 1400 EUR for 2 units
- DDAVP: 80 EUR for 40 µg
- Fibrinogen: 1000 EUR for 4g
- Tranexamic acid: 12 EUR for 2 g
- Protamin: 7 EUR for 5000 U
- Prothrombin complex concentrate: 300 EUR for 1800 U

What? How much? How often?

Prices depend on local conditions
Bleeding: therapeutic options

TRALI
- Plasma: 200 EUR for 2 units
- Platelets: 1400 EUR for 2 units
- DDAVP: 80 EUR for 40 µg

Fibrinogen: 1000 EUR for 4g

Thrombosis
- Tranexamic acid: 12 EUR for 2 g
- Protamin: 7 EUR for 5000 U

Prothrombin complex concentrate: 300 EUR for 1800 U

Risks:
- Sepsis
- TRALI
- Thrombosis
Problem: Low predictive value of standard laboratory tests in acquired coagulopathy

Pre-operative
British Journal of Haematology 2008;140:496-504

Intra-operative

Post-operative
Hematol J 2003;4:373-378
There is actually no sound evidence from well-designed studies that confirm the usefulness of standard laboratory tests for diagnosis of coagulopathy or to guide haemostatic therapy.
The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition

Rolf Rossaint\textsuperscript{1}, Bertil Bouillon\textsuperscript{2}, Vladimir Cerny\textsuperscript{3,4,5,6}, Timothy J. Coats\textsuperscript{7}, Jacques Duranteau\textsuperscript{8}, Enrique Fernández-Mondéjar\textsuperscript{9}, Daniela Filipescu\textsuperscript{10}, Beverley J. Hunt\textsuperscript{11}, Radko Komadina\textsuperscript{12}, Giuseppe Nardi\textsuperscript{13}, Edmund A. M. Neugebauer\textsuperscript{14}, Yves Ozier\textsuperscript{15}, Louis Riddez\textsuperscript{16}, Arthur Schultz\textsuperscript{17}, Jean-Louis Vincent\textsuperscript{18} and Donat R. Spahn\textsuperscript{19*}
We recommend that resuscitation measures be continued using a *goal-directed strategy* guided by standard laboratory coagulation values *and/or viscoelastic tests*. (Grade 1C)
Viscoelastic tests
Viscoelastic tests

comprehensive assessment of the coagulation process by the continuous measurement of blood clot firmness
Viscoelastic tests

“Thrombelastography”

“Thrombelastometry”

TEM / Werfen / Instrumentation Laboratory

ROTEM delta

ROTEM sigma

TEG 5000

TEG 6S

Hemosonics / Stago

Quantra

Haemonetics

ClotPro

enicor
Coagulation analysis in the PT / aPTT / TT / fibrinogen

coagulation activation

- thrombin
  - fibrin formation
  - platelet activation
  - polymerization
  - 3-dimensional network
  - fibrinolysis

Assessment in plasma

not assessed
coagulation activation

- thrombin
  - fibrin formation
  - platelet activation
  - polymerization
  - 3-dimensional network
  - fibrinolysis

Assessment in whole blood

> Viscoelastometry
Blood + reagents → Coagulation activation → Clot firmness → Clot stability or fibrinolysis → time

> Viscoelastometry
liver transplantation I

start of operation
Tranexamic acid

anhepatic phase

graft reperfusion
Tranexamic acid

end of surgery

liver transplantation II

start of operation
platelet transfusion

anhepatic phase

platelet transfusion

graft reperfusion

end of surgery
> Viscoelastometry: Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EX-tem / -test</td>
<td>Fast overview over the coagulation process</td>
</tr>
<tr>
<td>FIB-tem / -test</td>
<td>Functional detection of the fibrinogen level</td>
</tr>
<tr>
<td>AP-tem / -test</td>
<td>Assessment of coagulation with fibrinolysis inhibition</td>
</tr>
<tr>
<td>IN-tem / -test</td>
<td>Assessment of heparin, sensitive to FVIII</td>
</tr>
<tr>
<td>HEP-tem / HI-test</td>
<td>IN-test with heparin inhibition</td>
</tr>
<tr>
<td>TPA-test</td>
<td>Assessment of coagulation with fibrinolysis activation (ClotPro)</td>
</tr>
<tr>
<td>RVV-test</td>
<td>High sensitivity for new oral anticoagulants (NOACs) (ClotPro)</td>
</tr>
<tr>
<td>ECA-test</td>
<td>High sensitivity for direct thrombin antagonists (ClotPro)</td>
</tr>
</tbody>
</table>

Take home message:
Different assays evaluating different aspects of the coagulation system
Viscoelastometry: Treatment algorithm (example)

**ROTEM® Guided Coagulation Management**

- **EXTEM**
  - CT < 50s
  - MCF > 75mm
  - PROTHROMBOTIC
  - Anticoagulation?

- **FIBTEM**
  - CT > 75s
  - \(\alpha < 60^\circ\)
  - MCF < 50mm
  - HYPOCOAGULABLE
  - FFP 10-15ml/kg
  - PCC*

- **MCF**
  - > 10 mm
  - Platelet concentrate
  - < 10 mm
  - Fibrinogen 2-6g

- **APTEM**
  - MCF < 48mm
  - LYSIS > 15%
  - FIBRINOLYSIS
  - Tranexamic acid 10-15 mg/kg
Randomized controlled trial of 100 patients
   Elective complex cardiothoracic surgery with cardiopulmonary bypass
   (high risk patients)
   Enrolled after heparin reversal if at least one of these criteria met:
   Diffuse bleeding from capillary beds at wound surfaces
   Blood loss exceeding 250 mL/hr or 50 mL/10 min intraoperatively or in
   first 24 hours postoperatively
Conventional coagulation tests
Point of care tests
   ROTEM (viscoelastography)
   Multiplate (platelet aggregometry)
<table>
<thead>
<tr>
<th>Conventional Tests</th>
<th>Event</th>
<th>Point of Care Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT &gt;130 s</td>
<td>Protamine infusion</td>
<td>ACT &gt;130 s <em>AND</em> CT&lt;sub&gt;IN&lt;/sub&gt; &gt;240 s <em>AND</em> CT&lt;sub&gt;HEP&lt;/sub&gt;/CT&lt;sub&gt;IN&lt;/sub&gt; &lt;0.8</td>
</tr>
<tr>
<td>Preop fibrinogen &lt;200 mg/dL OR current fibrinogen &lt;150 mg/dL</td>
<td>Fibrinogen transfusion</td>
<td>A&lt;sub&gt;10EX&lt;/sub&gt; ≤40 mm <em>AND</em> A&lt;sub&gt;10FIB&lt;/sub&gt; ≤10 mm</td>
</tr>
<tr>
<td>INR &gt;1.4 OR APTT &gt;50 s</td>
<td>Prothrombin complex concentrate infusion</td>
<td>CT&lt;sub&gt;EX&lt;/sub&gt; &gt;80 s <em>OR</em> CT&lt;sub&gt;HEP&lt;/sub&gt; &gt;240 s</td>
</tr>
<tr>
<td>Transfusion of ≥4 units RBC without new results</td>
<td>Fresh frozen plasma infusion</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;80,000/μL OR suspected platelet dysfunction</td>
<td>Platelet concentrate transfusion</td>
<td>A&lt;sub&gt;10EX&lt;/sub&gt; ≤40 mm and A&lt;sub&gt;10FIB&lt;/sub&gt; &gt;10 mm <em>OR</em> TRAP &lt;50 AU ± ASPI &lt;30 AU ± ADP &lt;30 AU</td>
</tr>
<tr>
<td>Suspected platelet dysfunction</td>
<td>Desmopressin infusion</td>
<td>TRAP &lt;50 AU ± ASPI &lt;30 AU ± ADP &lt;30 AU</td>
</tr>
</tbody>
</table>

*Weber et al. Anesthesiology 117:531, 2012*
Fig. 3. Postoperative chest tube blood loss. POC = point-of-care.
<table>
<thead>
<tr>
<th>Table 6. Cumulative Costs of Transfused Allogenic Blood Products, Hemostatic Therapy (Including Coagulation Factor Concentrates), and Costs of Performed POC Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Group</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Allogenic blood products</td>
</tr>
<tr>
<td>Packed erythrocytes</td>
</tr>
<tr>
<td>[72 €/U]</td>
</tr>
<tr>
<td>FFP [0.162 €/g]</td>
</tr>
<tr>
<td>PC [231 €/U]</td>
</tr>
<tr>
<td>Other hemostatic therapy</td>
</tr>
<tr>
<td>Desmopressin [3.3 €/μg]</td>
</tr>
<tr>
<td>Fibrinogen [233 €/g]</td>
</tr>
<tr>
<td>PCC [11 €/600 IU]</td>
</tr>
<tr>
<td>rVIIa [2,784 €/240 kIU]</td>
</tr>
<tr>
<td>Total blood products and</td>
</tr>
<tr>
<td>hemostatic therapy</td>
</tr>
<tr>
<td>Expendable materials</td>
</tr>
<tr>
<td>POC Diagnostics</td>
</tr>
<tr>
<td>ROTEM®</td>
</tr>
<tr>
<td>Multiplate®</td>
</tr>
<tr>
<td>Cumulative [€]</td>
</tr>
<tr>
<td>Mean costs per patient [€]</td>
</tr>
</tbody>
</table>

Weber et al.
Anesthesiology
117:531, 2012
Use of viscoelastometry

Ideal result:

Less costs
(overall transfusions)

Better outcome
(less bleeding, less reexplorations)
Viscoelastometry: **Obstacles**

- Cost of the equipment
- Cost of the tests
- Who can do it?
- Quality management
- Who will understand the results?
Viscoelastometry: performance

**Cartridge based devices**
(ROTEM Sigma, TEG 6S, Quantra)

- Minimal user skills
- Cartridges of 4 assays (always run & pay 4 tests)
- Cost 60-100 EUR per cartridge (strongly depending on local conditions)

**Semiautomatic devices**
(ClotPro, ROTEM Delta, TEG 5000)

- Require pipetting
- Independent test channels (ClotPro: 6, ROTEM delta: 4, TEG 5000: 2)
- Cost 10-20 EUR per test (strongly depending on local conditions)
ClotPro

- 6 channels for parallel tests
- Newest viscoelastometry device

“active tip technology”
- Reagents present in the pipette tip
- No reagent handling

3 additional tests

**RVV-test:** detection of FX antagonists (Xarelto, Eliquis, Lixiana) and FII antagonists

**ECA-test:** detection of FII antagonist (Dabigatran, Argatroban), insensitive to FX antagonists

**TPA-test:** detection of antifibrinolytic agents (tranexamic acid)
Quality management

Quality control material available for all systems

If test is performed in a near-patient setting (OR – ICU) usually a cooperation with the laboratory is desirable
> Conclusions

Viscoelastometry is increasingly used for the management of complex coagulation disorders

Complex coagulation disorders:
• Acquired coagulation disorders
• Often combination of hemodilution + consumption of clotting factors
• Often in surgery and / or intensive case

Use of viscoelastometry can result in better management of bleeding complications, less transfusions and better outcomes