ROTEM and Human Fibrinogen Concentrate Use in Pediatric Cardiac Surgery

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Fibrinogen Structure

Fibrin Assembly

ROTEM
Rotational Thromboelastometry

- Based on the viscoelastic properties of whole blood
- Modification of the TEG (Thromboelastogram)
- Point-of-Care test for coagulation
- Results in 10 minutes
- Five Hemostatic assays
  - Fibrinogen and fibrin polymerization
  - Impact of coagulation factors
  - Hyperfibrinolysis
  - Platelet contribution

How It Works

ROTEM® is derived from “rotational thromboelastometry”, a powerful technique for the assessment of blood coagulation disorders.

Principle:
- Blood is added into a disposable cuvette (measuring cell) in a heated cuvette holder.
- Disposable pin (sensor) is fixed on the tip of a rotating shaft (axis).
- The rotating shaft is stabilized by a high precision ball bearing system.
- Shaft rotates back and forth 4.75 degrees.
- Shaft is connected to a spring to measure elasticity.
- Exact position of the shaft is detected by reflection of light on small mirror on the shaft.
- Data obtained from the reflected light is then computer processed into a graphical output.
**ROTEM® Experience**

Using Detailed Hemostasis Information

**Parameter** | **Definition** | **Information**
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Clotting Time, CT (sec) | Time to reach 2mm amplitude from beginning of test | Speed of fibrin formation, influenced by clotting factors, anti-coagulants
Clot Formation Time, CFT (sec) | Time to reach 2mm amplitude from the time of 2mm amplitude | Kinetics of clot formation, influenced by platelet level / function and fibrinogen level / ability to polymerize
Maximum Clot Firmness, MCP | Maximum amplitude (in mm) | Firmness of clot, i.e., clot quality influenced by platelets, fibrinogen concentration and ability to polymerize, Factor XIII, fibrinolysis
Maximum Lysis, ML (% of MCP) | Percent of clot firmness lost during measurement | Abnormal ML at 30 minutes likely indicates fibrinolysis

**ROTEM® Analysis**

ROTEM® provides the most complete and rapid information on hemostasis. Unlike standard clotting assays, ROTEM® analyzes whole blood and provides data about all stages of the coagulation process. The ROTEM® tests capture the specific hemostatic parameters below.

The results of the ROTEM® analysis should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient’s medical history, clinical picture and, if necessary, further coagulation tests.
BJA

Early thromboelastometry variables predict maximum clot firmness in children undergoing cardiac and non-cardiac surgery

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• Assessed 4,762 ROTEM tests in pediatric patients undergoing cardiac and non-cardiac surgery
  – Assessed correlation of MCF at 5, 10, 15 minutes to MCF
Results

- Strong correlation between A5, A10, A20 and MCF
- A5, A10, A20 strongly predictive of MCF in all ROTEM assays

100 patients
- Study group: 50 prospective
  - ROTEM transfusion protocol used
- Control group: 50 retrospective procedure and age matched patients.
- No transfusion protocol

Intraoperative Thromboelastometry Is Associated with Reduced Transfusion Prevalence in Pediatric Cardiac Surgery

Background: The majority of cardiac surgery patients receive blood transfusions. It is not uncommon that the initial use of intraoperative thromboelastometry (TE) guided transfusion decisions may reduce the overall proportion of patients receiving transfusions in pediatric cardiac surgery.

Methods: One hundred pediatric cardiac surgery patients were included in the study. Fifty patients were prospectively included and completed with 90 minutes of apheresis platelet transfusion at 60 and 120 minutes after surgery. In the study group, thromboelastometry, performed during cardiopulmonary bypass, guided the use of red blood cell transfusion and autologous blood donation. The intraoperative transfusion time was significantly reduced in the study group and the mean number of patients receiving blood products was significantly lower in the study group compared to the control group. Four main scenarios based on clinical observation and TEM results were possible.

- Insignificant bleeding—TEM: no transfusions
- Insignificant bleeding—abnormal TEM: no transfusions
- Significant bleeding—TEM: surgical intervention
- Significant bleeding—abnormal TEM: transfusion of blood products as indicated by a. hCT-TEM MCF ≤ 60 mm: platelets b. hCT-TEM MCF: ≤ 30 mm hydrogen concentrate c. hCT-TEM MCF: ≤ 30 mm FFP d. hCT-TEM MCF: > 60 mm FFP and/or platelets depending on MCF
Results

• ROTEM group: reduced proportion received transfusion of blood products
• Use of ROTEM changed transfusion pattern
  – Less patients received PRBC and FFP
  – More patients received Platelets and fibrinogen

Neonatal Coagulation

• Immature
• Fetal fibrinogen present until age 1
• Fetal fibrinogen is dysfunctional
• Neonatal fibrinogen has different electrical charge
• Higher phosphorous content than adult fibrinogen

Studies demonstrating immature neonatal coagulation


Coagulation Defects in Neonates During Cardiopulmonary Bypass

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We examined components of the coagulation system in 30 neonates (age, 1 to 30 days) undergoing deep hypothermic cardiopulmonary bypass (CPB). A coagulation profile consisting of activated clotting time; prothrombin time; partial thromboplastin time; factors II, V, VII, VIII, IX, X, and XII; fibrinogen; and platelet count; and hepatic levels was evaluated before bypass, at three intervals during bypass (1 minute after initiation of bypass, stable hypothermic CPB, warm CPB), after weaning from CPB and administration of protamine, and 2 to 3 hours after skin closure. The initiation of CPB resulted in a 50% decrease in circulating coagulation factors and anticoagulant II levels. Platelet counts were reduced by 70% with CPB initiation. Neither deep hypothermic temperatures nor prolonged exposure to extracorporeal surface had any additional effect on the coagulation profiles. This suggests that the coagulation system of a neonate undergoing CPB is profoundly and globally affected by hemodilution. We believe that treatment of post-CPB coagulopathy in neonates will address these global defects.

• Looked at 30 neonates
  - Assessed coagulation profile at 3 points during CPB and two points after CPB
• 50% decrease in coagulation factors and antithrombin III levels on CPB start
• 70% decrease in Platelets
• Conclusion
  - Coagulation system of neonates profoundly affected by CPB hemodilution

• Collected blood samples from neonatal cardiac patients at 3 points
  - Preop, after CPB initiation, after transfusion with cryoprecipitate
• Examined clots from patient samples or purified neonatal or adult fibrinogen with confocal microscopy

Fibrin Network Changes in Neonates after Cardiopulmonary Bypass
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ABSTRACT
Background: Quantitative and qualitative differences in the hemostatic systems exist between neonates and adults, including the presence of "fetal" fibrinogen, a quadruply disaccharidic form of fibrinogen that stems until 1 yr of age. The consequences of "adult" fibrinogen on clot structure in neonates, particularly in the context of surgery-associated bleeding, have not been well characterized. Here, the authors examine the sequential changes in clotting components and structure that ensue in a small sample of neonates undergoing cardiac surgery and cardiopulmonary bypass (CPB).

Methods: Blood samples were collected from neonates (n = 11) before surgery, immediately after CPB, and after the transfusion of cryoprecipitate (n = 3), adult fibrinogen (300 mg/kg) was also administered to 3 neonates. Clos were formed from patient samples or purified neonatal and adult fibrinogen. Clos structure was analyzed using confocal microscopy.

Results: Clots formed from plasma obtained after CPB and after transfusion were more porous than baseline plasmas. Analysis of clots formed from purified neonatal and adult fibrinogen demonstrated that equivalent fibrinogen concentrations, neonatal clots had a more dimensional structure, whereas adult clots were denser with significant three-dimensional structure. Clots formed from a combination of purified neonatal and adult fibrinogen were less homogenous than those formed from either purified adult or neonatal fibrinogen.

Conclusion: The results of this study confirm that significant differences exist in clot structure between neonates and adults and that neonatal and adult fibrinogen may not integrate well. These findings suggest that differential treatment strategies for neonates should be pursued to reduce the demonstrated morbidity of blood product transfusion.

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Conclusions

- Significant structural differences between neonatal and adult fibrin networks
  - Neonatal fibrin lacks 3D structure
  - More porous than adult
  - Highly aligned fibers
  - After CPB neonatal clots worsen
  - Not fully restored by adult fibrinogen

Human Fibrinogen Concentrate
RiaSTAP

- Indicated for acute bleeding in patients with congenital fibrinogen deficiency
- Approved by FDA 2009

**Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery**
A prospective randomised pilot study

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Prospective randomized trial
- Looked at 20 elective adult patients for CABG surgery
- Patients received either 2 g fibrinogen concentrate or placebo in OR just prior to incision

Significantly less blood loss (32%), higher Hg in fibrinogen group

Looked at graft patency by CT 3-4 days post-op
- no increased incidence of hypercoagulability
- no increased incidence of graft occlusion

Retrospective arm: 42 patients
- Developed standardized transfusion protocol based on bleeding and platelet count

The prospectively compared two groups (15 patients total) prospectively undergoing AV operation and ascending aorta replacement using transfusion protocol.
- Group 1 no fibrinogen
- Group 2 received prophylactic HFC before protocol started (Removal of aortic X-clamp)
  - Targeted FIBTEM MCF to 22 mm

Fibrinogen group had reduced bleeding & transfusion requirements.
• Prospective, randomized controlled trial in 63 children less than 7 undergoing elective cardiac surgery
  – Randomized to receive 60 mg/kg HFC or cryoprecipitate 10 mL/kg after protamine administration, if fibrinogen low.
• Results
  – HFC as efficacious and safe as cryoprecipitate in the treatment of bleeding children after cardiac surgery

Retrospective study
• Looked at 100 pediatric cardiac surgery patients
  – Group 1: first 50 patients who received HFC (70 mg/kg)
  – Group 2: age, size and procedure matched cohort from the pre-HFC era
• Assessed blood loss and transfusion requirements
• Assessed LOS and thrombotic events

Results
• In HFC treated group significantly less:
  – cryoprecipitate (11 cc/kg vs. 2 cc/kg)
  – FFP (61 cc kg vs. 39 cc/kg)
• No difference in incidence of thrombotic events
• Significant reduction in fibrinogen level at time of rewarming compared to pre-op value
  – 114 mg/dL vs. 225 mg/dL
Correlation study

- Looked at 50 charts to obtain 87 data points where fibrinogen levels were paired with FIBTEM MCF
- Linear regression analysis demonstrated significant positive linear relationship (p<0.0001) between fibrinogen levels and FIBTEM MCF

\[ \text{Predicted fibrinogen} = 78.61 + 12.38 \times \text{MCF} \]

It suggests that 1 mm of increase in MCF corresponds to an average increase of 12.38 mg/dL in the fibrinogen level.

Interval Changes In ROTEM Values During CPB

- Retrospective
- Attempted to define and quantify how various interventions, i.e., CPB, transfusion with component blood therapy, use of HFC affect the ROTEM values
- Presented at CCAS/SPA meeting March 2018
Interval Changes In ROTEM Values During CPB

- Intervention I: CPB
- Intervention II: Administration of PLT given during the rewarming phase of CPB
  - Median dose of 38 ml/kg.
- Intervention III: administration of Protamine, and HFC (70 mg/kg) after CPB termination.
- Intervention IV: further component therapy if bleeding persisted after the HFC and ROTEM indicated a deficiency. This could be further HFC, PLT, FFP or cryoprecipitate.

Interval Changes In ROTEM Values During CPB

- ROTEM 1: Baseline Value
  - obtained at the start of surgery prior to CPB initiation.
- ROTEM 2: On CPB
  - during the rewarming phase, prior to PLT administration
- ROTEM 3: on CPB
  - after PLT administration.
- ROTEM 4: after CPB termination
  - after protamine and HFC administration.
- ROTEM 5: after the administration of other blood products if bleeding persisted

Results

- 161 patients
  - Three groups
    - 90 days less
    - 90 days to 2 years
    - Older than age 2
Prospective randomized trial
Phase 1

Looked at 30 neonates and infants divided into two groups
Group 1 - 70 mg/kg HFC
Group 2 - Placebo

Conclusion

• Transfusion with PLT median dose 38 cc/kg
  - HEPTEM α: ↑ by 22°
  - FIBTEM MCF: ↑ by 3 mm
• Treatment with HFC (70 mg/kg)
  - FIBTEM MCF: ↑ by 3 mm
  - Fibrinogen conc. ↑ by 73 mg/dL

Transfusion Algorithm

- Administration of HFC
- Reversing thrombin
- Fibrin platelets
- HEPTEM
- FIBTEM
- Platelet transfusion
- Conversion to PLT
- Reversing
- Administration of HFC
- Reversing thrombin
- Administration of HFC
- Administration of HFC
- Administration of HFC
- Administration of HFC
Transfusion Protocol

PRBC: Volume required = Blood volume (V) x desired Hct increase / Hct of red cell unit (70%)

FFP: 20 cc/kg
Plateletpheresis: 20 cc/kg
Cryoprecipitate: 10 cc/kg

Primary endpoints

• Total peri-operative blood loss for first 24 hours post-op (cc/kg)
• Identity and volume of transfused blood products (cc/kg)
• Hg 2 and 24 hours post op

Secondary Endpoints

• Hours of post-op vent support
• LOS CICU
• LOS hospital
• Need for re-exploration for bleeding within first 12 hours post-op

Adverse Events

• Signs of central or peripheral thromboembolism
  - includes catheter or vessel occlusion
• Respiratory or Circulatory failure
• Allergic reactions
Prospective randomized trial
Phase 2

- Will look at another 30 neonates and infants divided into two groups
- Group 1 - 70 mg/kg HFC
- Group 2 - 140 mg/kg HFC

The End
Not Quite

Pictures of Jorge

After School Activity