Fibrinogen replacement therapy in acquired perioperative bleeding

Sibylle Kietaibl

in collaboration with
Arash Afshari, Aamer B. Ahmed, Daniel Bolliger,
Rachel Collis, Anne-Sophie Ducloy-Bouthors,
Susan M. Goobie, Thorsten Haas, Marcus D. Lancé,
Barto Nascimento, Vojislava Neskovic,
Marco Ranucci, Christoph J. Schlimp,
Kenichi A. Tanaka, Anne Juul Wikkelsø

UNI-MED

Fibrinogen replacement therapy in acquired perioperative bleeding

UNI-MED

UNI-MED Verlag AG
Bremen - London - Boston

Kietaibl, Sibylle:
Fibrinogen replacement therapy in acquired perioperative bleeding/Sibylle Kietaibl.-
1st edition - Bremen: UNI-MED, 2018 (UNI-MED SCIENCE)
ISBN 978-3-8374-6392-7

MEDICINE - STATE OF THE ART

UNI-MED Verlag AG, one of the leading medical publishing companies in Germany, presents its highly successful series of scientific textbooks, covering all medical subjects. The authors are specialists in their fields and present the topics precisely, comprehensively, and with the facility of quick reference in mind. The books will be most useful for all doctors who wish to keep up to date with the latest developments in medicine.

Preface and acknowledgements

Fibrinogen is a crucial molecule in humans with an extraordinary role in stopping and preventing bleeding: it is the substrate of clots. Fibrin networks in robust clots protect mankind against main causes of death in young age groups – maternal death due to peripartum haemorrhage (PPH) and exsanguination due to trauma-induced coagulopathy (TIC). Fibrinogen secures patient outcome during and after major surgical procedures in all age groups from neonates to frail elderly.

Fibrinogen is our coagulation factor No.1 – it would be worthwhile to declaring at least one calendar day as "fibrinogen day". As a substitute, this book is dedicated to fibrinogen!

Internationally accepted experts donated their time gratuitously and shared their expertise and knowledge in their respective book chapters. As the initiator of our successful book project I express my gratitude to you, dear collaborators. My thanks also go to Dr. Wulfmeyer, editor of UNI-MED, for his professional support of our fibrinogen book coup. Last, but not least my thanks go to you, dear readers, for your interest. I hope that our compilation of fibrinogen replacement will allay your curiosity and thirst for knowledge.

Vienna, June 2018 *Sibylle Kietaibl*

Authors

Arash Afshari, M.D., Ph.D.,
Head of Research
Department of Pediatric and Obstetric Anesthesia
Juliane Marie Center
Rigshospitalet
University of Copenhagen
Blegdamsvej 9
DK-2100 Copenhagen
Denmark

Chapter 10.

Aamer B. Ahmed, MD FRCA FACC FESC
Department of Anaesthesia
Glenfield Hospital, University Hospitals of Leicester NHS Trust
Groby Road
Leicester LE9 2ER
United Kingdom

Chapter 8.

Daniel Bolliger, MD
Department for Anesthesia
Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy
Basel University Hospital
Spitalstrasse 21
CH-4031 Basel
Switzerland
Email: Daniel.Bolliger@usb.ch

Chapter 2.

Rachel Collis
Department of Anaesthetics and Pain Control
Cardiff & Vale University Health Board
Cardiff
UK
Email: Rachel.Collis@wales.nhs.uk

Chapter 5.

Anne-Sophie Ducloy-Bouthors
Pole anesthésie-réanimation
Maternité Jeanne de Flandre, Academic Hospital
Avenue Oscar Lambret
59037 Lille
France
Email: anne-sophie.bouthors@chru-lille.fr

Chapter 5.

Susan M. Goobie, MD, FRCPC
Associate Professor of Anaesthesiology
Harvard Medical School Associate in Perioperative Anesthesia
Clinical Director, Pharmacokinetics Laboratory
Dept. of Anesthesiolgy, Critical Care & Pain Medicine
300 Longwood Ave, Boston Children's Hospital
Boston, MA 02115
USA
Email: Susan.Goobie@childrens.harvard.edu

Chapter 6.

Thorsten Haas, MD
Professor of Anaesthesiology
Department of Paediatric Anaesthesia
University Children's Hospital Zurich
Steinwiesstrasse 75
CH-8032 Zurich
Switzerland
E-Mail: thorsten.haas@kispi.uzh.ch

Chapter 6.

Sibylle Kietaibl, MD, MBA
Professor of Anaesthesiology
Department of Anaesthesia and Intensive Care
Evangelical Hospital Vienna
Hans-Sachs-Gasse 10-12
A-1180 Vienna
Austria
E-Mail: s.kietaibl@ekhwien.at

Chapter 1.

Marcus D. Lancé
Department of Anesthesiology and perioperative medicine
Hamad Medical Corporation
Doha
Qatar

Chapter 9.

Barto Nascimento
Sunnybrook Health Sciences Centre
2075 Bayview Ave., Room H1 71
Toronto, ON, M4N 3M5
Canada

Chapter 8.

Vojislava Neskovic, MD, PhD, DEAA
Military Medical Academy
Belgrade
Serbia

Chapter 4.

Marco Ranucci
Department of Cardiothoracic Vascular Anesthesia and Intensive Care
IRCCS Policlinico S. Donato
Piazza Edmondo Malan, 2
I-20097 San Donato Milanese
Italy

Chapter 3.

PD Dr. Christoph J. Schlimp
Department of Anaesthesiology & Intensive Care
Evangelical Hospital Vienna
Hans-Sachs-Gasse 10-12
A-1180 Vienna
Austria

Chapter 7.

Kenichi A. Tanaka, MD, MSc
Department of Anesthesiology
University of Maryland School of Medicine
22 South Greene Street, Suite S8D12
Baltimore, Maryland 21201
U.S.A.
Email: ktanaka@som.umaryland.edu

Chapter 2.

Anne Juul Wikkelsø, MD, PhD
Department of anaesthesia and intensive care medicine
Hvidovre Hospital
Kettegård Alle 30
DK-2650 Hvidovre
Denmark

Chapter 10.

Contents

1. Introduction

What Can Be Expected in the Following Nine Book Chapters?

Hypofibrinogenaemia is the grey eminence behind all chapters. Normal ranges of fibrinogen levels and hypofibrinogenaemia have been defined; fibrinogen levels can be measured in blood samples.

In **Chapter 2.** K. Tanaka et al. describe easy to digest pathophysiology of bleeding. This chapter highlights differences between acquired and inherited hypofibrinogenaemia. When considering the pathophysiological role of fibrinogen as the polar star for clinical decision-making, it appears self-evident to correct acquired hypofibrinogenaemia in order to produce stronger clots, reduce blood loss, and allogeneic blood transfusion requirements.

Key message in **Chapter 3.** by M. Ranucci is fibrinogen replacement in acquired perioperative hypofibrinogenaemia< 1.5 g/L in cardiac surgery: when to replace, when not to replace, and how to replace fibrinogen. Noteworthy, cardiac surgical bleeding has been selected in recent international licensing trials of various companies manufacturing fibrinogen concentrates. Some were successful, some failed. This brilliant chapter may open our eyes for potential flaws in study designs, e.g., adequate timing and dosing or ignoring the prerequisite for replacement - which is hypofibrinogenaemia.

Time is life: In **Chapter 4.** Neskovic highlights the importance of speedy diagnostics and speedy therapy in the life-threatening situation of severe trauma-dependent bleeding. Fibrinogen can be depleted very early and fast in TIC. Fibrinogen is the usual suspect for timely substitution before other coagulation factors need replacement. Viscoelastic haemostatic assays (VHA) permit speedy diagnostics of the actual demand for fibrinogen replacement as well as fibrinogen-independent bleeding sources. This exciting chapter demonstrates the shift in bleeding management: from blind, not goal-directed, not individualized, allogeneic blood product-based bleeding management towards a targeted, coagulation factor concentrate-based approach with a restrictive and transfusion trigger-based use of allogeneic blood products.

Hyperfibrinolysis is the common problem in TIC and PPH. Fibrin and fibrinogen are designed to be dissolved by plasmin-dependent fibrino(geno) lysis which is the basis for later (after-clotting) recanalisation of injured vessels, re-perfusion, and finally wound healing. Excessive lysis (hyperfibrinolysis), however, breaks down clots too early resulting in ongoing bleeding. Anti-fibrinolytic drugs are required to prevent fibrinogen consumption – before fibrinogen replacement.

Chapter 5. is dedicated to PPH as a pathophysiological model of hyperfibrinolysis and defibrination. A. Ducloy-Bouthors and R. Collis in their chapter highlight the fact that normal ranges of fibrinogen are much higher upon delivery as well as the predictive value of hypofibrinogenaemia for the progression of PPH and for failure of balloon compression, requiring surgical escalations up to hysterectomy for bleeding control. For practical implementation this chapter offers a protocol for VHA-targeted fibrinogen replacement.

As simple as that: a) severe bleeding in our youngest population is an emotional clinical situation and b) critical low fibrinogen levels can accelerate bleeding in infants and children. In **Chapter 6.** S. Goobie and T. Haas describe crystally clear that fibrinogen is the first coagulation factor that achieves critical low levels. Although the Clauss assay is globally established to assess fibrinogen levels in the paediatric population, functional fibrinogen activity in VHA (specifically the FIBTEM measuring the fibrinogen contribution to clot strength) is assessed much faster, almost in real time. VHA has been shown to be effective in guiding paediatric perioperative bleeding management.

In **Chapter 7.** C. Schlimp describes current sources of fibrinogen for replacement: by transfusing plasma (FFP), cryoprecipitate or by infusing fibrinogen concentrate. Plasma and cryoprecipitate traditionally serve as the main sources of fibrinogen replacement worldwide despite poor evidence to support any benefit for the prophylactic or therapeutic use of these blood components to correct hypofibrinogenaemia.