

Surgery – a challenge in haemophiliacs with inhibitors

M. Serban¹; D. Poenaru¹; L. Pop¹; H. Ionita¹; D. Mihailov¹; N. Tepeneu¹; R. Badeti¹; D. Lighezan¹; W. Schramm²

¹Victor Babes University of Medicine and Pharmacy, Timisoara, Romania;

²Hemostaseology, Ludwig-Maximilians University, Munich, Germany

Keywords

Haemophilia, inhibitors, surgery

Summary

Treatment of haemophiliacs with inhibitors is of great concern in low-income countries confronting shortage in substitutive treatment. Invasive interventions on these patients represent a major challenge due to the fact that costs are significantly higher in comparison to similar procedures conducted on patients without inhibitors. **Objective:** In the context of insufficient availability of clotting factor, we aimed at highlighting the experience of surgical treatment in inhibitor patients. We analyzed the indications, types of performed interventions and outcomes. **Patients, methods:** This single center, retrospective analysis has been conducted on 7 inhibitor patients registered and treated in Haemophilia Center of Timisoara over ten years (1997–2007): six patients with severe hemophilia A (3 – high titer, 3 – low titer), one patient with von Willebrand disease (low titer). Three patients developed inhibitors only after 2–5 days post surgery. **Results:** A total of 15 invasive procedures were carried out: 2 orthopedic interventions (1 arthrodesis, 1 arthroscopic synovectomy), 2 urogenital interventions (1 surgical testicular detorsion, 1 orchiectomy), 4 limb amputations (2 bilateral upper and 2 lower limb amputation), 2 pseudotumour (PT) surgery interventions, 5 drainages (2 massive pyohaemothorax, 1 drainage of shank haematoma, 1 drainage of compressive forearm haematoma, 1 drainage of thigh haematoma). Haemostasis was achieved in patients with low level inhibitors (< 5 BU/ml) with high doses of FVIII concentrates; in those with high inhibitor

level (> 5 BU/ml), surgery was managed using by-passing agents. Supplementation with local fibrin glue and intravenous or local antifibrinolytic agents was given in 68.75% of interventions. Postoperative complications consisted of haemorrhagic shock in 13.33% of interventions and infection in 6.66%. Haemostatic outcome was evaluated by blood loss and duration of treatment, compared to expectations for non-inhibitor patients. The outcome was excellent and good in 66.66% of interventions, and fair in 33.33%. **Discussion, conclusion:** Indication of invasive procedures in haemophiliacs with inhibitors was limited to life and/or limb-threatening situations. In low-income countries, inhibitor and recovery of FVIII monitoring is mandatory in the postoperative follow-up of patients with low or no substitution prior to surgery due to false negative results at the preoperative investigation.

Schlüsselwörter

Hämophilie, Antikörper, Chirurgie

Zusammenfassung

Die Behandlung von Hämophilie-Patienten mit Inhibitoren ist ein reales Problem in Ländern mit niedrigem Einkommen und Mangel in der Substitutionstherapie. Invasive Eingriffe stellen eine Herausforderung dar, da die Kosten im Vergleich zu den ähnlichen Verfahren bei Patienten ohne Hemmkörper, viel höher sind. **Ziel:** Im Rahmen der unzulänglichen Verwendbarkeit der Gerinnungsfaktorenkonzentrate, streben wir an, die Erfahrung der chirurgischen Behandlung bei Patienten mit Hemmkörper hervorzuheben. Wir analysierten die Indikationen, Interventionen und Ergebnisse. **Patienten, Methoden:** Diese retrospektive Studie bezieht sich

auf sieben Patienten mit Hemmkörpern über zehn Jahre (1997–2007): Sechs Patienten mit schwerer Hämophilie A (drei mit hohem, drei mit niedrigem Titer), ein Patient mit von-Willebrand-Erkrankung (niedriger Titer). Drei der Patienten entwickelten die Hemmkörper erst 2–5 Tage nach dem chirurgischen Eingriff. **Ergebnisse:** 15 operative Eingriffe wurden durchgeführt: orthopädische (Arthrodesis: 1, arthroskopische Synovectomie: 1), urogenitale (Detorquierung bei Hodentorsion: 1, Orchiektomie: 1), beiderseitige Oberschenkelamputation: 2 und Unterschenkelamputation: 2, Entfernung von Pseudotumoren: 2, Drainage eines massiven Pyohaemothorax: 2, andere Drainagen: 3 (je ein Unterschenkel-, Unterarm-, Oberschenkelhämatom). Bei Patienten mit niedrigem Hemmkörpertiter (< 5 B.E./ml), Blutstillung wurde mit hochdosierten FVIII-Konzentraten erreicht; bei denen mit einem Bethesdatiter > 5 B.E./ml wurde die Hämostase durch die intravenöse Applikation von Bypassing-Agenten gesichert. Lokale Fibrinpreparate und intravenöse Antifibrinolysemitel wurden in 68,75% der Eingriffe verwendet. Komplikationen: hämorrhagischer Schock (13,33%) und Infektion (6,66%). Blutstillung wurde mit Hilfe zweier Kriterien ausgewertet: Blutverlust und der Behandlungsdauer, verglichen mit Erwartungen für Patienten ohne Hemmkörper. Bei Berücksichtigung beider Kriterien war das Ergebnis in 66,66% sehr gut und gut, in 33,33% der Eingriffe zufriedenstellend. **Diskussion, Schlussfolgerung:** Operative Eingriffe bei Hemmkörperpatienten wurde auf die lebensbedrohende Situationen begrenzt. In Ländern mit niedrigem Einkommen ist postoperativ die strenge Überwachung von Hemmkörpern und Substitutionstherapie (FVIII-Aktivität im Plasma, In-vivo-Recovery) bei Patienten mit geringer oder ohne Substitutionstherapie vor dem chirurgischen Eingriff unentbehrlich. Grund: falsch negative Ergebnisse bei der präoperativen Untersuchung.

Correspondence to:

Prof. Dr. Margit Serban
Children's Hospital Louis Turcanu
3rd Paediatric Clinic, Dr. I. Nemoianu Street No. 2
Timisoara, 300011, Romania
Tel. +40/256/29 59 77, Fax +40/256/29 59 78
E-mail: mserban@spitalcopiitm.ro

Chirurgie – eine Herausforderung bei Hemmkörperpatienten

Hämostaseologie 2009; 29 (Suppl 1): S39–S41

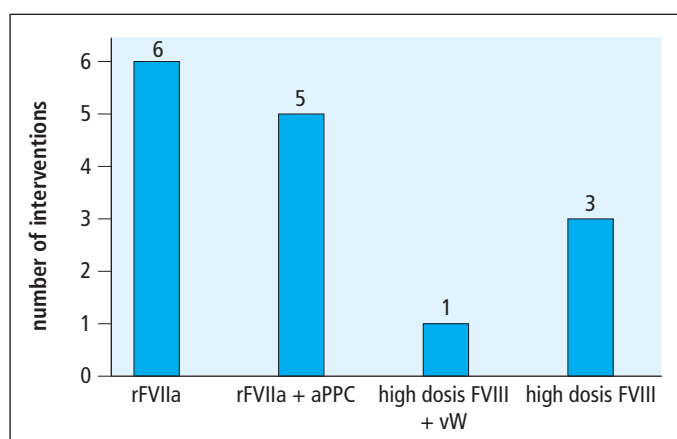


Fig. 1
Treatment regimens

Treatment of haemophiliacs with inhibitors is of great concern in low-income countries confronting shortage in substitutive treatment. Invasive interventions on these patients represent a major challenge due to the fact that costs are significantly higher in comparison to similar procedures conducted on patients without inhibitors (1).

In the context of insufficient availability of clotting factors, we aimed at highlighting the

experience of surgical treatment in inhibitor patients.

Patients and methods

This single center, retrospective analysis has been conducted on 7 inhibitor patients registered and treated in Haemophilia Center of Timisoara over ten years (1997–2007):

- 6 patients with severe hemophilia A (3 – high titer, 3 – low titer),
- 1 with von Willebrand disease (low titer).

Mean age: 13 ± 4.64 (range: 5–22 years). Three patients developed inhibitors only after 2–5 days post surgery. We analyzed the indications, types of performed interventions and outcomes.

The invasive procedures consisted of: orthopaedic, urogenital interventions, limb amputation, pseudotumour surgery, drainages (shank, thigh and compressive forearm hematoma, pyohaemothorax). Synovectomy was performed in recurrent haemarthroses (> 3/month) and arthrodesis in the presence of severe pain estimated by the pain score according to the World Federation of Hemophilia (WFH) and highly damaged joint, followed by postoperative drainage for 1–2 days. Extensive release was associated in one patient with severe flexion contracture. In 80% of cases the interventions were emergencies.

Haemostasis was achieved in patients with low level inhibitors (< 5 BU/ml) with high doses of FVIII concentrates under FVIII-recovery control (► Tab. 1); in those with high inhibitor level (> 5 BU/ml), surgery was managed using bypassing agents: recombinant FVIIa (rFVIIa) or activated prothrombin complex concentrates (aPCC), as single agent or in combination according to WFH recommendations (2) (► Fig. 1, ► Tab. 1). Supplementation with local fibrin glue and intravenous or local antifibrinolytic agents was given in 68.75% of interventions.

In our experience, a judicious reduction of factor concentrates starting with day 2 post-surgery (owing to financial burden, reasons for cost-efficiency and/or shortage of factor concentrates), namely factor concentrates administration only in perilous postoperative periods (during wound dressing/drainage tube positioning) may not only significantly reduce the blood loss but also the amount of substitution without unfavorable impact on evolution (4).

Rehabilitation started on the second day postsurgery and continued up to 90–180 days. Average hospitalization days were 19.6 ± 6.138 . Haemostatic outcome was evaluated by two criteria (3): blood loss and duration of treatment, compared to expectations for non-inhibitor patients (► Tab. 2).

Tab. 1 Substitution with high doses of FVIII, aPCC and of rFVIIa

dosage	procedure	preoperative	day 1–5	day 6–14
FVIII	minor	50–80 IU/kg	40–60 IU/kg q 8h day 1 30–40 IU/kg q 12 h day 2–5	-
	intermediate/ major	100–120 IU/kg	50–60/kg q 6h day 1 40–80 IU/kg q 8h day 2–5	20–30 IU/kg q 12h day 6–8, q 24h day 9–14
aPCC	minor	50–75 IU/kg	50–75 IU/kg q 12–24h 1–2 doses	-
	intermediate	75–100 IU/kg	75–100 IU/kg q 8–12h	75–100 IU/kg q12h
	major	75–100 IU/kg	75–100 IU/kg q 8–12h	75–100 IU/kg q12h
rFVIIa	minor	90–120 µg/kg	2–4 × 90–120 µg/kg	-
	intermediate/ major	120 µg/kg	90–120 µg/kg q 2h day 1 q 3h day 2, q 4h day 3–5	90–120 µg/kg q 6h

Tab. 2 Evaluation of haemostatic outcome compared to expectations for non-inhibitor patients

haemostatic outcome	blood loss (BL)	duration of treatment (DoT)
excellent	normal or lower than normal BL	normal or shorter than normal DoT
good	no exceeding with more than 10% of normal BL	no longer than an excess of 10% of normal DoT
fair	10–30% more than normal BL	10–30% longer than normal DoT
poor	> 30% more than maximal of normal BL	> 30% longer than max of normal DoT

Results

A total of 15 invasive procedures were carried out (► Fig. 2): 2 orthopaedic interventions (1 arthrodesis, 1 arthroscopic synovectomy), 2 urogenital interventions (1 surgical testicular detorsion, 1 orchietomy), 4 limb amputations (2 bilateral upper and 2 lower limb amputation), 2 pseudotumour (PT) surgery interventions, 5 drainages (2 massive pyohaemothorax, 1 drainage of shank haematoma, 1 drainage of compressive forearm haematoma, 1 drainage of thigh haematoma). According to severity of interventions we considered 11 of them major, 3 intermediate and 1 minor.

Haemostatic outcome evaluated by blood loss and duration of treatment, compared to expectations for non-inhibitor patients, was

- excellent in 40% of interventions (1 testicular detorsion, 1 orchietomy, 1 arthroscopic synovectomy, 1 drainage of thigh haematoma, 2 bilateral upper limb amputation),
- good in 26.66% (1 drainage of forearm haematoma, 1 knee arthrodesis, 2 lower limb amputation) and
- fair in 33.33% (2 drainage of pyohemothorax, 2 pseudotumour surgery, 1 drainage of shank haematoma).

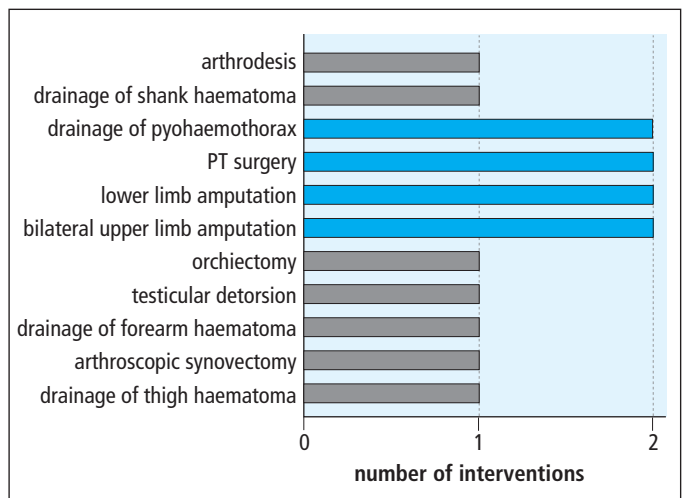
Transfusion of red blood cells was necessary in 7 interventions (46.66% of cases). Postoperative complications consisted of haemorrhagic shock in 13.33% of interventions and infection in 6.66%. Treatment regimens were well tolerated.

The total cost of surgery in patients with haemophilia A and inhibitors was at least fourfold higher compared to c surgery in haemophilia patients without inhibitors (5).

Discussion, conclusion

Indication of invasive procedures in haemophiliacs with inhibitors in our center was

Fig. 2
Invasive procedures



Tab. 3 Costs of surgical interventions

haemophilia patients	total average costs of surgical interventions
without inhibitors	22 866.66 ± 10 216.76 €
with inhibitors	62 333.33 ± 29 825.417 €

limited to life and/or limb-threatening situations. Most interventions were performed as emergency surgery, elective surgery being postponed or discouraged.

In low-income countries, inhibitor and recovery of FVIII monitoring is mandatory in the postoperative follow-up of patients with low or no substitution prior to surgery, due to false negative results at the preoperative investigation. Bleeding and progressively reducing of FVIII-recovery preceded the diagnosis of inhibitors in 3 of the 7 patients. Anamnestic reaction should be anticipated after 3–14 days of substitutive treatment, and alternative forms of therapy should be preserved (5, 6). Antifibrinolytic drugs (tranexamic acid or e-aminocaproic acid) and fibrin glues in local application should be used as adjuvant therapy to reduce the amount of recombinant FVIIa or activated prothrombin com-

plex concentrates needed for haemostatic control.

Conflict of interest

All authors declare that there is no conflict of interest.

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