Combined (sequential and parallel) therapy with by-passing agents and antifibrinolytics in patients with hemophilia and inhibitor.

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Objectives:

Patients with hemophilia A and high titer of inhibitor are certainly difficult to manage. Approximately 10 - 20 % of bleeding episodes cannot be controlled effectively and safely using one of the by-passing agents, recombinant activated factor VII (rFVIIa, Novoseven®) or activated prothrombin complex concentrate(APCC, FEIBA ®). Sometimes, the dose increase and the shortening of intervals, is not sufficient and neither is switching to the other agent.

Combined (sequential and parallel) therapy is considered a "salvage" regimen. Our objectives were to analyze our experiences with combined therapy.

Methods:

We retrospectively collected data about our institution patients who received combined by-passing therapy. There were 4 adult patients (aged 52-59), all having hemophilia A with high titer of inhibitor (6.6-269.0 Bethesda units/ml). All of them were HCV positive and received antiviral treatment. From January 2010 until November 2013 there were 13 bleeding episodes for which we used combined treatment. 12 were sequential treatment (alternating between the two by-passing agents in different length) and 1 was parallel treatment (APCC 50 IU/kgBW at 12 hours intervals, rFVIIa 120 micrograms/kgBW at 3 hours intervals, with 3-6 hour intervals between them).

Results: table

Patient No.	Bleeding episode No.	Type of therapy	Site of bleeding	Reason for dual therapy	Regimen	Clinical outcome	Complications
1	1	Parallel	Intracerebellar haemthoma	Neurological deterioration	Days 1-4 – rFVIIa 130 mcg/BW Days 5-6 – aPCC 50 UI / BW bid + rFVIIa 130 mcgr/ BW at 6 h intervals Days 7-11 - rFVIIa 130 mcgr/ BW at 6 h intervals Days 12-15 - observation	Neurological improvement CT scan – decreased dimensions of haemathoma	Neurological sequelae (Vertigo)
1	2	Sequential	Soft tissue haemathoma of the thoracic wall and the arm	Insufficient quantity of medications	Days 1-3 – aPCC 50 UI / BW at 8 h intervals Days 4 - rFVIIa 90 mcgr / BW at 3 h Days 5-7 - rFVIIa 90 mcgr / BW 1 hour before physical therapy	Complete recovery	No
1	3	Sequential	Bleeding in the shoulder	Insufficient quantity of medications	Days 1-2 - rFVIIa 90 mcgr / BW at 3 h Days 3-4 - aPCC 50 UI / BW at 12 h intervals	Complete recovery	No
1	4	Sequential	Bleeding in the soft tissues of the hand	Insufficient quantity of medications	Days 1-2 - rFVIIa 90 mcgr / BW at 2 h Day 3 - aPCC 50 UI / BW at 12 h intervals	Complete recovery	No
1	5	Sequential	Gasrointestinal bleeding	Insufficient quantity of medications	Days 1-2 - rFVIIa 90 mcgr / BW at 2 h Day 3 -10 aPCC 50 UI / BW at 12 h intervals	Complete recovery	No
1	6	Sequential	Extraction of 4 teeth	Insufficient quantity of medications	Day 1 - rFVIIa 90 mcgr / BW at 2 h Day 2 - rFVIIa 90 mcgr / BW at 4 h Day 3 – aPCC 50 UI/BW at 12 h intervals	Intervention without bleeding	No
1	7	Parallel	Macrohaematuria	Increased fibrinolytic activity	Days 1-4 -- rFVIIa 90 mcgr / BW at 2 h intervals Day 5 - rFVIIa 90 mcgr / BW at 6 h intervals Days 1-7 – tranexamic acid 1 gr every 8 h per os	Complete recovery	No
1	8	Sequential	Bleeding in the soft tissues of the neck	Insufficient quantity of medications	Day 1 - rFVIIa 90 mcgr / BW at 2 h intervals Days 2- 6 - aPCC 50 UI/BW at 12 h intervals	Complete recovery	No
2	9	Sequential	Extraction of 5 teeth	Insufficient quantity of medications	Days 1-3 -- rFVIIa 90 mcgr / BW at 2 h intervals Days 4-7 - aPCC 50 UI / BW at 12 h intervals Days 1-7 EACA 5 gr at 12 h intervals per os	Intervention without bleeding	No
2	10	Sequential	Head trauma (temporoparietal haemthoma)	Insufficient quantity of medications	Day 1 - rFVIIa 110 mcgr / BW at 2 h intervals Days 2- 3 - aPCC 50 UI/BW at 8 h intervals Days 4-7 - aPCC 50 UI/BW at 12 h intervals	Complete recovery by CT scan	No
3	11	Sequential	Gastrointestinal bleeding (gastric Dielafoy lesion)	Insufficient quantity of medications	Day 1 – Endoscopic local therapy (fibrin glue and hemocliping locally) and rFVIIa 90 mcgr / BW at 2 h intervals Day 2 - aPCC 50 UI/BW at 8 h intervals	Complete recovery	No
4	12	Sequential	Serious nose bleeding	Inefficacy of one medication (?)	Day 1 - tamponada nasi Days 1-2 - aPCC 50 UI/BW at 6 h intervals Days 3-4 no therapy Day 5 – detamponada Days 6-8 - rFVIIa 90 mcgr / BW at 2 h intervals Plus surgicel tampon locally	Complete recovery	No
4	13	Sequential	Ileopsoas and intragluteal haemathomas	Inefficacy of one medication	Days 1-4 - aPCC 50 UI/BW at 6 h intervals Days 5-10 - - rFVIIa 90 mcgr / BW at 2, 4, 6 h intervals	Recovery with pseudocysts	No

Conclusions:

Even though it is not easy to determine whether bleeding had resumed, we believe combined therapy was successful in all of the cases. There were clear clinical and radiological improvements, most often with complete recovery. The combined (sequential and parallel) therapy with by-passing agents and antifibrinolytics in our patients with hemophilia and inhibitor were safe and effective, but it should be used only as a "last resort" salvage therapy.

DOI: 10.3252/pso.eu.WFH2014.2014