Sicke Cell Disease

A pilot study on the efficacy of ketorolac plus tramadol infusion combined with erythrocytapheresis in the management of acute severe vaso-occlusive crises and sickle cell pain

One of the major causes of hospitalization for patients with sickle cell disease (SCD) are vaso-occlusive crises (VOC), which are characterized by acute pain and organ damage related to the presence of dense red cells. Here we report a pilot study which combined balanced analgesia with tramadol plus ketorolac and erythrocytapheresis.

haematologica 2004; 89:1389-1391
(http://www.haematologica.org/2004/11/1389)

Pain is the major hallmark of vaso-occlusive crises (VOC) caused by sickle cell disease (SCD) and is generated by somatic, neuropathic and vascular mechanisms.[1-4] Recent guidelines for pain management suggest balanced analgesia to improve the efficacy of treatment and to reduce the adverse side effects of each drug[5,6] The strategy of balanced analgesia is based on the co-administration of drugs with different pharmacological mechanisms of action, controlling pain of different origins. The co-administration of tramadol and ketorolac has been reported to be a valid balanced analgesia in acute pain syndromes (e.g. post-operative pain, trauma).[7] Tramadol, an atypical opioid, has particular pharmacological characteristics. It acts on mu-receptors and potentiates the mono-aminergic system acting on the re-uptake of mono-aminergic mediators at the level of the inhibitory pain pathways.[8] Moreover, tramadol has a better safety profile than the major opioids particularly since it causes less respiratory depression.[9]

Another important issue in the management of acute VOC is the transfusion strategy, some aspects of which still remain controversial. The development of automated red blood cell (RBC) exchange, or erythrocytapheresis has largely simplified the use of RBC-exchange. Erythrocytapheresis can rapidly produce the desired percentage of HbS (usually ≤ 30%), control blood volume exchange better, increase arterial oxygen pressure and improve blood visco-elastic parameters. Although erythrocytapheresis is currently recommended in severe acute complications of SCD, its use is still controversial in retinal infarction and pain crises.[10] In this pilot study we evaluated the impact of a new analgesic regimen, with continuous infusion of ketorolac and tramadol associated with erythrocytapheresis in the management of severe acute VOC pain in SCD patients.

Seven adult SCD patients aged between 16 and 3 years old were enrolled. There were four males and three females; 4 were Caucasian and 3 were black-Africans. None had co-inherited α-thalassemia and none was being treated with hydroxyurea. The patients were followed from January 2000 to January 2004. Each hospitalization for VOC was defined as an episode and scores for various parameters were recorded on admission and at 3, 12, 48, and 72 hours. The scores were evaluated on a visual analog scale (VAS) from 0 to 10. The parameters assessed were: (i) pain level: 0 (no pain) to

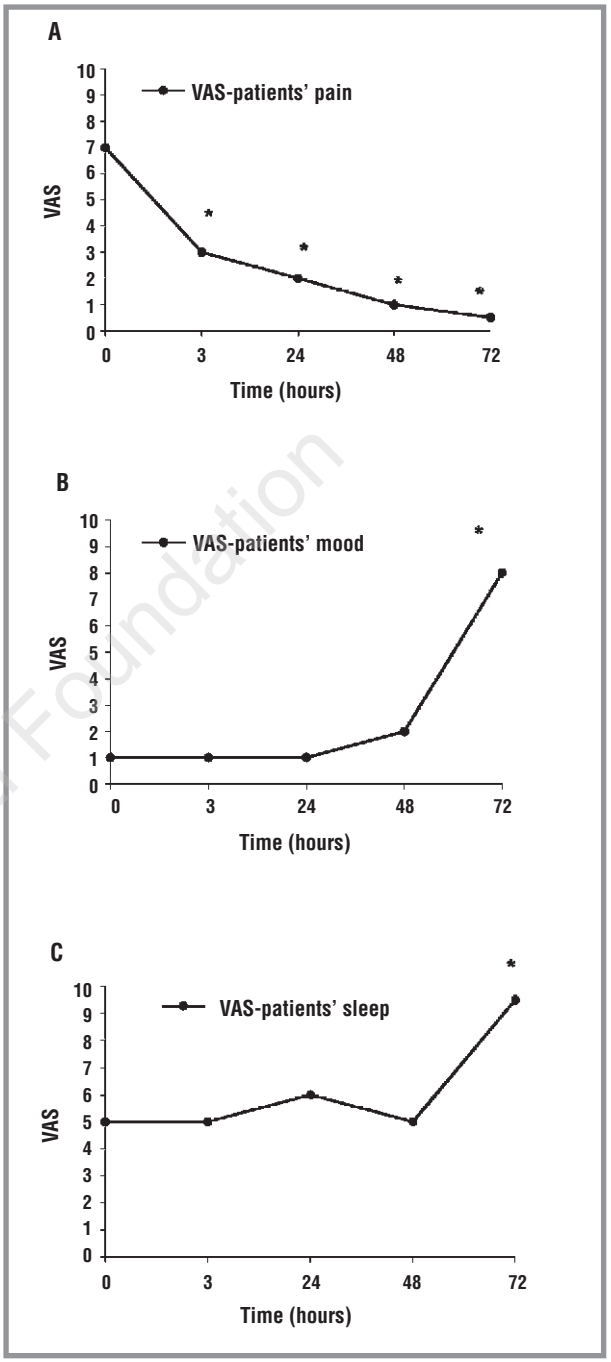

Figure 1. Visual analog scale (VAS) of patients' (A) pain, scored from 0 (no pain) to 10 (worst possible pain); (B) mood, scored from 0 (worst mood) to 10 (best mood); and (C) quality of sleep, scored from 0 (no sleep or worst sleep) to 10 (best sleep). Data are reported as medians of the observations (n=29); *$p<0.05$ compared to baseline, considered as time 0.

Table 1. Sickle cell patients' hemoglobin and hemoglobin S values before and after erythrocytapheresis (TEA) procedures.

	Acute VOC				*7-10 days after*			
Pt	*pre-TEA-Hb (g/dL)*	*post-TEA-Hb (g/dL)*	*pre-TEA-HbS (%)*	*post-TEA-HbS (%)*	*pre-TEA-Hb (g/dL)*	*post-TEA-Hb (g/dL)*	*pre-TEA-HbS (%)*	*post-TEA-HbS (%)*
1	9.8±41.6(6)	9.8±1.1(6)	66.2±18.3(6)	30.2±4.7(6)*	10.2±1.0(6)	10.6±1.5(6)	43.4±5.9(6)°	19.5±8(6)*
2	9.3±1.2(4)	10±1.3(4)	51.5±9.9(4)	25.9±9.0 (4)*	9.8±0.2(4)	9.7±0.7(4)	47.3±2.5(4)	27.8±9.9(4)*
3	9.2±1.5(4)	10.0±1.1(4)	64.5±3.9(4)	15.1±3.2(4)*	10.0±0.3(4)	9.3±0.2(4)	39.3±3.2 (4)	15.6±0.5(4)*
4	10.8±0.6(3)	9.5±1.0(3)	55.5±14.8(3)	35.6±8.1(3)*	11.1±1.2(3)	10.9±1.1(3)	45.6±2.5(3)	26.6±1.1(3)*
5	10.2±1(6)	11.1±0.8(6)	63.3±7.6(6)	22.1±7.2(6)*	10.7±0.8(6)	9.7±0.6(6)	37.6±4(6)	29.3±1.2(6)*
6	9.8±1.3(3)	10.8±0.8(3)	61.2±10(3)	29.1±5.2(3)*	9.7±0.6(3)	10.1±0.9(3)	42±3.6 (3)°	31.3±1.7(3)*
7	10.6±0.6(3)	10.4±2.2(3)	62.9±15(3)	16.0±7.4(3)*	9.6±0.5(3)	9.8±1.0(3)	44.5±2.9(3)°	14.6±8.0(3)*

*Pt: patient; pre-TEA Hb: hemoglobin pre-erythrocytapheresis; post-TEA-Hb: hemoglobin post-erythrocytapheresis; pre-TEA-HbS: sickle hemoglobin pre-erythrocytapheresis; post-TEA-HbS: sickle hemoglobin pre-erythrocytapheresis. Data are presented as means±SD (n of determinations). *p< 0.05 compared to pre-treatment values; °p<0.05 compared to post-treatment values.*

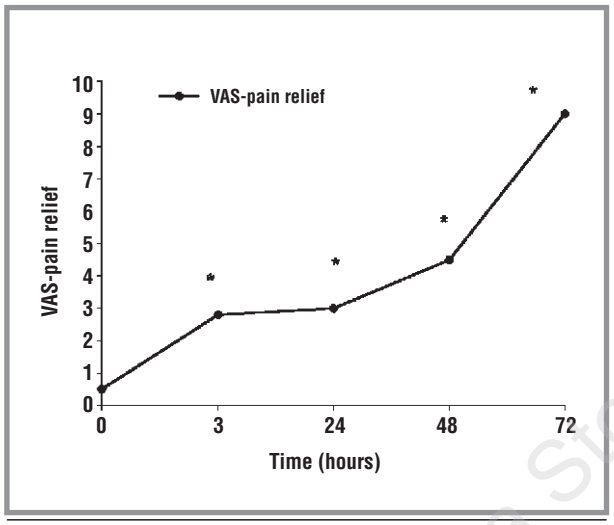

Figure 2. Patients' pain relief evaluated by a visual analog scale (VAS) scored from 0 (no relief) to 10 (complete pain relief). Data are reported as medians of the observations (n=29); *p<0.05 compared to baseline, considered as time 0.

10 (worst pain); (ii) patient's mood: 0 (worst mood) to 10 (best mood); (iii) patient's sleep: 0 (no sleep or worst sleep) to 10 (best sleep); pain relief: 0 (no relief) to 10 (complete pain relief). The severity of the VOC was determined by adding the first three VAS scores. When this value was equal or lower than 15, the VOC episode was define as severe. The duration of the VOC episode, the type of analgesic therapy and its duration were recorded. The primary outcomes were pain relief, the length of hospital stay measured in days and pain management failure.

Pain management protocol: a combination of ketorolac 0.86 mg/kg/day, tramadol 0.3 mg/kg/hr and metoclopramide 0.57 mg/kg/day was continuously infused for a maximum of 72 hours. We considered pain management to be a failure if tramadol had to be replaced by morphine. The incidence of the following side-effects was recorded: nausea, vomiting, drug-induced gastritis, peptic ulcer disease, respiratory depression, renal failure.

Erythrocytapheresis protocol: erythrocytapheresis was performed between 12 and 24 hours after the hospitalization and repeated 7-10 days later. The RBC used for erythrocytapheresis were matched for Rh, C, E and Kell antigens and were leukodepleted and fresh (≤ 14 days old). Erythrocythapheresis was performed on a 3rd-generation continuous-flow system COM.TEC (Fresenius, Biofil, Germany) with double venous access, maintaining isovolemia.

The co-administration of tramadol and ketorolac was effective in all VOC, as shown by the patients' pain relief which was consistent with their expectations, and by the significant improvement of the patients' mood and sleep (Figures 1 and 2). These data suggest that ketorolac effectively controlled incident type pain, while tramadol acted on the nociceptive pain component, but also on vascular and neuropathic pain. No changes in peripheral oxygen saturation were observed during tramadol plus ketorolac administration (SpO2 ranged between 96.5 and 98%, n=29). There were no side effects in any patient and no failure of balanced analgesia was observed.

As shown in Table 1, the percentage of HbS dropped significantly but transitorily after eythrocytapheresis in all patients. The double procedures, ensuring durable removal of different sickle red cell subpopulations, might prevent further amplification of vaso-occlusive tissue damage and most likely promote faster tissue repair. Thus, the shorter hospitalization of patients managed with the present protocol compared to their historical data for VOC episodes (10.8±0.7 days, n= 28 vs 6.9±1.5 days, n=29; p<0.05) may be related to the beneficial effects of balanced analgesia combined with the maintenance of low HbS levels.

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Key words: sickle cell disease, therapeutic erythrocytapheresis, HbS, visual analog scale, vaso-occlusive crisis.

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Bone Marrow Transplantation

Elevated thrombopoietin levels and alterations in the sequence of its receptor, c-Mpl, in patients with Diamond-Blackfan anemia

In the study of the possible thrombopoietin (TPO)-c-Mpl pathway involvment in the pathogenesis of Diamond-Blackfan anemia, repeatedly increased serum TPO levels were identified in 7/14 patients and changes in c-mpl sequence in 3/14 patients. While elevated TPO levels can represent a compensatory mechanism for impaired erythropoiesis, c-Mpl mutations could influence the disease severity.

haematologica 2004; 89:1391-1392
(*http://www.haematologica.org/2004/11/1391*)

Thrombopoietin (TPO) is the major stimulator of megakaryopoiesis and platelet production.[1] Besides its function in megakaryopoiesis, TPO and its receptor c-Mpl are also involved in the production of progenitors of other hematopoietic lineages.[2] TPO acts synergistically with erythropoietin, greatly expanding the number of erythroid progenitors *in vitro*, as well as in mice after myelosuppressive therapy.[3] Its plasma level is inversely correlated to the mass of megakaryocytes and platelets, which degrade TPO following its binding to c-Mpl.[1]

Diamond-Blackfan anemia (DBA) is a congenital red cell aplasia characterized by normochromic macrocytic anemia, reticulocytopenia, normocellular bone marrow with a selective deficiency of erythroid precursors, normal or slightly decreased leukocyte count, and normal or slightly increased platelet count.[4] To elucidate the possible role of the TPO-c-Mpl pathway in the pathogenesis of DBA we measured TPO serum levels and screened *c-mpl* for mutations in these DBA patients.

In 7/14 (50%) of DBA patients, serum TPO levels were repeatedly higher than in age-matched controls (Table 1). Two of three patients with a mutation in RPS19 also showed elevated TPO levels. Interestingly, all patients had normal or slightly changed platelet counts, indicating that the general TPO level control mechanism may be altered in DBA patients and/or the increase in the TPO level may represent a compensatory mechanism for the promotion of their impaired

Table 1. Characteristics of DBA patients with increased plasma TPO levels.

Patient (sex)	*Age (years)*	*Type of anemia (treatment)*	*Associated anomalies*	*Platelet count (×10⁹/L)*	*Plasma TPO (pg/mL)*	*Age-matched controls (pg/mL); Average±SD*	*Mutation in RPS19*	*Mutation in c-mpl*
CZ2 (M)	28	mild (S)	thenar hypoplasia	225	215; 221; 259	52±20.7 n = 22	no	no
CZ3 (F)	21	remission	kidney aplasia	174*	178; 199	52±20.7 n = 22	no	Leu524Leu (C1570T)ˣ Val556Phe (G1666T)
CZ7 (F)	14	severe (TD)	no	174	215; 252; 278	52±20.7 n = 22	G167A R56Q	no
CZ9 (F)	18	mild (S)	no	293	178; 211; 235	52±20.7 n = 22	Del(196-206) frameshift	no
CZ19 (M)	8	mild (S)	short stature	530*	209; 215	88.4±19.5 n = 7	no	no
CZ21 (M)	5	severe (TD)	no	290*	239; 245; 390	80.5±23,8 n = 7	no	Val114Met (G340A)#
CZ23 (F)	3	severe (TD)	no	139*	304; 338; 589	90.8±29.1 n = 9	no	no

*TPO levels in all of these patients were at least 6 standard deviations above the average level in age-matched controls. Individual c-mpl exons were amplified by polymerase chain reaction (PCR); amplicons were purified and used as templates for sequencing using an ABI310 Genetic Analyzer (Perkin Elmer). Nucleotide numbering: A in the first start codon is considered +1. TD: transfusion dependency; S: steroid dependency; *: increased platelet count in infant age; x: mutations in the same allele (proved by PCR cloning of the region spanning exons 11 and 12, and by sequencing); #: the same substitution found also in a patient with a normal level of TPO; SD: standard deviation.*