Sickle Cell Disease

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Background :

Sickle cell disease (SCD) is a life-threatening genetic disorder affecting nearly 100 000 individuals in the United States, more than 10 000 in UK and millions worldwide. It is estimated that each year approximately 300,000 infants are born worldwide with a major hemoglobinopathy.

- **Incidence:**
Patients with sickle cell disease report pain on 54.5% of days and 60 % of patients with SCD have at least one severe pain by year

- **Clinical presentation** (summary):
SCD is associated with many acute and chronic complications requiring immediate medical attention. Severe acute pain is the commonest manifestation of SCD requiring hospital admission in Europe and the USA. Although the pain itself is not directly life threatening, inappropriate treatment leads to unnecessary suffering and potentially fatal complications, related both to the disease and the treatment, and repeated admissions with pain are associated with a higher mortality rate.
Vaso Occlusive Crisis (VOC) is not only responsible for pain but also for a large panel of complications. Among them is the occlusion of central artery of the retina, priapism and different wounds which are difficult to heal. More life threatening complication as acute chest syndrome is out of the scope of this report.

- **Standard management (summary) and outcome (HBO excluded)**
According to most recent guidelines published in 2014 and 2015 in peer reviewed journals, the management of SCD patients has to be done in a multidisciplinary way.

The 2014 Evidence-based report by expert panel published in JAMA states that the recommendations with a strong strength for management of a vaso occlusive crisis are:

- Rapidly initiate treatment with parenteral opioids (high quality of evidence (QE))
- Use incentive spirometry during hospitalization to reduce the risk of acute chest syndrome (moderate QE)

And with moderate strength of recommendation:

- Continue NSAID's treatment if pain is moderate and this treatment has proven to be efficacious for this patient (low QE)
- Initiate around-the-clock opioid administration by patient-controlled analgesia (low QE)
- Do not administer a blood transfusion unless there are other indications for transfusion in children and adults with a vaso occlusive crisis (low QE)

Rationale for HBO use

Haemoglobin S polymerisation and red cell sickling under deoxygenated conditions are central in the pathophysiology of vaso occlusive crisis. Recently, Kaul and al promoted the idea that the interaction between sickle red cell and endothelium through adhesion proteins could be a major initiating factor of vaso occlusion. Limiting sickling by limiting hypoxemia, HBOT should reduce this factor. Furthermore it has been shown that HBO down regulates ICAM-1 which expression is increased in adhesive process (Buras 2000)

Evidence – Based review of HBO use

- **Low level evidence :**

Non controlled clinical studies (case studies, …)

There are only case reports and one case serie study on the effect of HBO on pain in VOC. This later showed a drastic reduction of pain and of morphine consumption with HBO on 9 patients.

Case reports show also a benefit of HBO in other symptoms due to SCD, as priapism in a child, occlusion of central artery of the retina, osteomyelitis or ulcers. All of these reports show the inocuity of HBOT

Conclusion : Recommendation

For the moment, hyperbaric oxygen is not included in the protocols to treat crisis during evolution of sickle cell disease. Nevertheless, it is recognized that these crisis are numerous and that actual therapeutic has not such a good rate of success. Opioids which are in first line, have a lot of secondary effects in this situation as they have to be used at very high doses. To rapidly initiate opioids is the only recommendation of the protocol with a high level of quality evidence. One can wonder if this high level isn't due to the term "rapidly" more than for opioids. Much more can be done to bring relief to the painful SCD patient. It is well recognised that deoxygenation of red cell favors sickling and adhesive reaction with vascular endothelium and so far VOC. Hyperbaric oxygen can play on this factor.

As there is strict and clear protocols for the management of VOC, and that these protocols don't give a high success rate, we suggest that these protocols can be followed with a second arm adding HBOT. As there are very few complications due to HBOT (much less than for opioids) it is an ethically acceptable proposal. We should be able to show a reduction in opioids use, in delay for reaching EVA less than 3 and finally a reduction in hospital stay or readmission.

The case reports published show a huge difference between HBOT and non-HBOT groups. The balance between desirable and undesirable effects is very high in favour of HBOT. In this aspect, the recommendation to make studies is strong although of low quality evidence.

Study	Type	Nb Patients	Aim(s)/ Evaluation criteria	Inclusion / Exclusion criteria	HBO Protocol (pressure, time, nb of sessions)	Results	Conclusion / comments
Altmann IA et al. Int Wound J 2015	patho physiology		Algorithm for treatment	leg ulcers in SCD patients			
Buras JA et al Am J Physiol Cell Physiol 2000;278:C292-C302	In Vitro					downregulation of ICAM-1 expression by hypoxia	
Pszolla N et al Clinical Infect Dis 2003;37:e78-82	CR	1		ulcer of Buruli after 5 months unsuccessful treatments		healed in 3 weeks	dissemination osteomyelitis. HBOT successful on local cicatrisation
Smith WR Annals Int Med 2008;148:94-101	Prospective cohort study	232	report of pain in adults			pain on 54.5%	pain is more prevalent and severe than usally thought
Raphael JL Ped Blood Cancer 2008;51:398-401	retrospective cohorte study	2 x 35	compare Day Hospital vs Inpatient management of VOC				in favor of day hospital management
Ender KL Ped Blood Cancer 2014;61:693-6	Prospective clinical study		Assess the usefulness of a clinical pathway				good analysis of pain

Kaul DA Microcirculation 2009;16:97-111	review invitro studies						role of SC- Endothelium interaction in adhesion process
Yawn BP JAMA 2014;312(10):1033-1048	Guidelines Expert Panel		Chronic SCD and acute crisis				Management protocols grading evidence based
Habibi A La Revue de Médecine Interne 2015;36:5S3-5S84	Guidelines						French guidelines with flyers for each item
Rees DC Br J Haemat 2003;120:744-52	Guidelines		acute painful crisis				NBO only if Sat<95% don't mention HBO
Humphreys JVA J Family Med Primary Care 2012;1(1):56-8	Guidelines		primary care setting				no mention of Oxygen
Minniti CP Am J Hematol 2015;00:1-9	review		Treatment leg ulcer in SCD				no advantage of HBO but not argued
Brandow AM Ped Blood Cancer 2011; 56:789	retrospective cohorte study	19	Impact of multidisciplinary pain management	SCD pain inpatients children			decreased SCD pain hospitalizations
Mychaskiw II J Clin Anesth 2001;13:255-258	Prospective invitro study		Effects of HBO on cell morphology			no effect on morphology of sickle cells, invitro	
Canan H J Med Case Reports 2014;8:370	CR	1	Central retinal artery occlusion	25 years old	2.5 ATA 2x/d for 7 days and 1x/d for 6 days	improvement of visual acuity	HBOT beneficial

Murray SJ Ped Inf Dis J 2002;21(10):	CR	1	Fusobacterium osteomyelitis	7 yrs old	not available		HBOT beneficial
Reynolds JDH JAMA 1971;216(12):1977-8	CR	1	painful abdominal crisis	25 yrs	2 ATA 90 mn		good effect immediately but definitive only after third session
Renaudier P Transf Clin Biolo 2014;21:178-81	review physiopathology SCD						
Azik FM Turk J Hematol 2012;29:270-3	CR		priapism	11 yrs 72h after onset with automated red cell exchange	2.5 ATA 90 mn 11 sessions	complete detumescence, no reoccurance after 4 years	
Ballas SK Clin Hemorheology Microcirculation 2015						topography of membrane affects adhesion	
Ballas SK Blood 2012;120(18):3647-56							treat crisis as earlier as possible. tPA, NO
Solovey A J Clin Invest 1998;101(9):1899-1904	invitro study						tissue factor expression
Stirnmann J Div Hyperb Med 2012;42(2):82-	retrospective cohorte study	9	Vaso occlusive crisis				feasible and effective to reduce pain