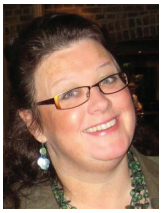

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Sickle Cell Disease, Dentistry and Conscious Sedation

Abstract: The features of sickle cell disease (SCD) are described. Two case reports of patients treated in a Dental Institute are presented and the dental management of patients with SCD discussed. Since infection is one of the major risk factors for sickle cell crisis, the prevention of oral disease and infection is vital for this group of patients and there is no contra-indication to the delivery of dental treatment under local anaesthetic with inhalational sedation if required in the primary care setting. Since patients with sickle cell disease are particularly vulnerable to the effects of periods of hypoxia, which may produce significant morbidity, and because of the additional practical challenges in sedating this group of patients, intravenous sedation should be undertaken in a specialist unit.

Clinical Relevance: The increasing prevalence of sickle cell disease highlights the importance of dentists practising in multi-cultural communities having an understanding of this condition and its implications on their clinical practice. This will facilitate the safe management of patients with sickle cell disease.

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Sickle cell disease is a hereditary chronic anaemia, which results from the production of defective sickle haemoglobin, HbS, instead of normal haemoglobin, HbA. The gene for HbS production is autosomal recessive, thus an individual inheriting two HbS genes (a homozygote) is said to suffer from sickle cell disease, whilst a heterozygote with only one HbS gene has sickle cell trait. Sickle cell trait has such innocuous features that it does not require treatment and does not affect lifespan. These individuals are usually asymptomatic and rarely display the physical abnormalities or anaemia seen in those with sickle cell disease. In this paper, the term sickle cell disease will therefore be used to describe only the homozygous condition.[1]

Haemoglobin is a globular protein molecule, composed of two pairs of polypeptide chains, each intricately folded around a haem molecule. Haemoglobin A (HbA) consists of two α and two β chains. The β globin chain contains 146 amino acids and the two genes determining β chain structure are located on the short arm of chromosome 12. Genetic information is coded by the sequence of nucleotides; three bases (a codon) represent the basic unit of information and determine a single amino acid on the globin chains. Sickle haemoglobin (HbS) results from a single point mutation, where the normal codon, *GAG*, at position 6 on the β chain is replaced by *GUG*. This change results in the substitution of valine (in HbS) for the glutamic acid that occurs at this position in HbA. This single base substitution results in the tendency of deoxy HbS molecules to form polymers and hence the production of the symptoms of sickle cell disease.[2]

Incidence

Sickle cell disease is found in many populations and parts of the world historically associated with malarial endemicity. People of Afro-Caribbean, West African, Asian and Northern Greek descent are most commonly affected. It is generally accepted that the presence of a single sickle gene (in sickle cell trait) confers relative protection against the malaria-causing parasite *Plasmodium falciparum* during the critical phase of early childhood, between the loss of passively acquired maternal immunity and the development of actively acquired immunity. During this period children with sickle cell trait are less likely to die from malaria and consequently they are more likely to survive and reproduce, passing on their genes.[2] As a result of population migration, this and other haemoglobinopathies are

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now amongst the most common inherited disorders within North-West Europe. In 1997, Streetly *et al* estimated that there were approximately 12,500 people in the UK with sickle cell disorders.[3]

Pathophysiology of erythrocyte sickling

Early observations of the sickling process revealed that haemoglobin within the sickled cell appeared to aggregate into foci and that this was followed by collapse of the cell membrane. Erythrocytes in individuals with sickle cell disease will begin to sickle at oxygen tensions less than 40 mm Hg.[4] Even in normal circumstances, red cells arriving at the capillaries and venules give up enough oxygen to the tissues to initiate this sickling. A period of 2–4 minutes at this reduced oxygen tension is, however, required to produce marked erythrocyte distortion. Under normal physiological conditions, red cells are only in the venous circulation for 15 seconds, so sickling is not a problem.[4,5] In areas of vascular stasis, however, where the circulation is slowed and erythrocytes are exposed to low oxygen tension for a prolonged period, sickling may occur.[5]

Once the red cells become sickled, a cascade of events follows. The sickled cells are stiff and irregularly-shaped, with an increased surface area, which increases blood viscosity, and retards blood flow.[5] Capillary transit time and oxygen consumption is consequently increased and erythrocytes are therefore exposed to greater periods of hypoxia and a vicious cycle ensues with further sickling and stasis.[2] This results in the occlusion of blood vessels, with subsequent tissue infarction, hence the end-organ pathology seen in sickle cell disease.

Factors precipitating the sickling process

In addition to hypoxia, episodes of sickling and vaso-occlusion may be precipitated in affected individuals by infection, fever, dehydration, acidosis, exposure to extreme cold, emotional stress or rigorous exercise. The mechanism by which infection precipitates a painful crisis remains obscure, but it is thought that this is likely to be multi-factorial with fever, dehydration and acidosis all contributing, although there is some evidence that these crises may occur because of pyrexia alone. It is difficult to assess and quantify the effect of emotional stress, but the occurrence of painful crises during examinations or accompanying times of difficulty at home or work is not uncommon.

CNS	- CVA - cranial nerve neuropathy
Cardiac	- cardiomegaly - heart failure
Respiratory	- pulmonary infarction - pulmonary hypertension - acute chest syndrome
Skeletal	- pain - bone marrow infarction - osteomyelitis, usually *Salmonella* infection - aseptic necrosis of femoral head - dactylitis
Immune	- susceptibility to infection - autosplenectomy
Hepatic	- jaundice - liver infarction - bilirubin gall stones - hepatomegaly - liver dysfunction
Renal	- renal infarction - renal failure - inability to concentrate urine - priapism
Other	- leg ulceration - retinopathy, blindness - haemaolytic anaemia - reticulocytosis

Table 1. The systemic effects of sickle cell disease.

Clinical features of sickle cell disease

SCD is associated with pathological changes which affect almost every organ or body system (Table 1) and is characterized by recurrent 'crises' which may be painful or haematological. The painful vaso-occlusive crisis is one of the most characteristic manifestations of sickle cell disease, producing severe pain (described as deep and boring) of several days or even up to two weeks' duration. Such painful crises are thought to result from the avascular necrosis of bone marrow, the inflammatory reaction to which results in increased intramedullary pressure, producing excruciating pain. Pain is most frequently experienced in the articular areas of the long bones, lumbar spine and pelvis; however crises producing pain in the jaws have been reported.[6]

Aplastic crises resulting in profound depression of erythropoesis

have been associated with parvovirus infection in the patient with sickle cell disease. A mean fall in Hb level of 4g/dl is observed, with the spontaneous recovery of bone marrow usually being seen within ten days. Folic acid deficiency may produce a megaloblastic crisis, resulting in suppressed erythropoesis. Sequestration crises are seen in children, in whom vast amounts of red blood cells are sequestered in the spleen, resulting in precipitous drops of Hb level.

The efficiency of the immune system is significantly reduced in patients with sickle cell disease. Impaired macrophage phagocytosis, defective opsonization and altered complement pathways, together with functional asplenia (by the age of six) resulting from repeated sickling within the spleen render patients prone to infection, particularly by encapsulated bacteria which, in healthy individuals, are usually cleared from the body by the spleen.[4]

General management

Patients with sickle cell disease have their haematological state monitored regularly by haematologists. Daily prophylactic penicillin is given from infancy to help to prevent infection, since most of the encapsulated bacteria which cause significant morbidity and mortality in patients with sickle cell disease are sensitive to this drug. Immunization against life-threatening infection by *Pneumococcus* and *Haemophilus influenzae B* is also undertaken. Folic acid supplementation is given to ensure that effective erythropoeisis is maintained and megaloblastic crises are prevented.[7]

Children and other patients considered to be at high risk of recurrent cerebral vascular accidents (CVAs) are managed with regular exchange transfusions to maintain an HbS concentration of 30% or less. The prevention of iron overload for such patients is essential. Bone marrow transplantation can 'cure' sickle cell disease, if the patient can survive graft-versus-host disease, but even with a well-matched familial donor the mortality rate is 10%.[4]

The prevention of painful crises by patients and healthcare professionals avoiding precipitating factors such as hypoxia, infection, dehydration and cold is essential. Painful, vaso-occlusive crises must be managed promptly with analgesia (including opiates), fluid therapy, warmth and antibiotics, if necessary.

Dental care for patients with sickle cell disease

Since infection is one of the major risk factors for sickle cell crisis, the prevention of oral disease and odontogenic infection is of primary importance in patients with sickle cell disease.[8,9] A rigorous preventive regime must be implemented as early as possible. This should include oral hygiene instruction, regular professional cleaning, dietary advice and the appropriate use of fluoride application and fissure sealants.[8]

Routine dentistry should only be undertaken in non-crisis periods,[8,9] with any treatment during a crisis being restricted to pain relief and the elimination of infection. Since it is known that both physical and emotional stress may contribute to the onset of a sickle cell crisis, wherever possible appointments should be in the early morning and kept as brief as possible.[5,9]

The need for antibiotic prophylaxis for patients with the disease who are undergoing dental treatment is unclear. The degree of immunosuppression of patients with sickle cell disease (especially those who have undergone splenectomy or who are hyposplenic) is so significant that some authors recommend the administration of pre-operative antibiotics for all dental procedures likely to produce a bacteraemia, since this may result in sepsis and a crisis.[4,5] Other authors however, advise the use of such prophylaxis only for patients undergoing oral surgery procedures (since these are more likely to result in infection) to minimize the incidence of subsequent osteomyelitis.[2,8,9] There is no evidence or common recommendation regarding the choice of antimicrobial agents to provide such prophylaxis, but Lawrenz in 1999 stated that this should cover the oral flora and encapsulated organisms.[4] The antibiotic prophylaxis should, however, be of low toxicity, short duration, have good activity against commensal oral pathogens and take into account the likely existing daily penicillin prophylaxis which may promote the carriage of penicillin-resistant oral streptococci. For adult patients with no evidence of allergy to beta-lactam antibiotics, a single dose of Co-amoxiclav 500 mg, taken orally an hour before surgery, would appear to represent an appropriate regime. Penicillin allergic patients should be given 200 mg doxycycline and 400 mg metronidazole orally prior to the procedure.

Analgesia

The control of dental pain using paracetamol or codeine is widely advocated since the use of aspirin or non-steroidal anti-inflammatory drugs may have an adverse effect on the acid-base balance, promoting acidosis and sickle cell crisis.[8,10] In addition, this group of analgesics may impair kidney function and exacerbate any pre-existing renal damage caused by repeated sickling within the kidneys.

Local anaesthesia

Theoretically, the vasoconstrictor in local anaesthetic solution may produce hypoxia and vascular stasis in the area of injection, which could promote sickling. Its use, however, has been widely reported to be free of any major complications[4,7] and there appears to be no real evidence that local anaesthetic solution with vasoconstrictor is contra-indicated in patients with sickle cell disease.

General anaesthesia

General anaesthesia for patients with sickle cell disease is universally described as hazardous and its use should be avoided wherever possible. There will of course, however, always be occasions when a dental patient cannot be managed under local anaesthetic or sedation and, in these situations, general anaesthesia may be unavoidable. The change in oxygen partial pressure, blood flow, pH and lowered temperature which accompany the anaesthetic may promote intravascular sickling and hence a painful, vaso-occlusive crisis.[10]

When a patient with sickle cell

disease undergoes general anaesthesia, the prevention of hypothermia, hypovolaemia, hypotension, hypoxia and acidosis are described as the most crucial management considerations.[11] Prior to the induction of anaesthesia, 5 minutes of pre-oxygenation has been recommended to ensure any transient hypoxia that occurs can be tolerated without morbidity.[4,12]

Conscious sedation

Inhalational sedation using a mixture of oxygen (O_2) and nitrous oxide (N_2O) is acknowledged to be of great benefit to those with sickle cell disease who are anxious about dental treatment.[2,5] Its anxiolytic effects reduce stress and, throughout the procedure, the inspired oxygen concentration always exceeds that of air, thus minimizing the risk of sickling.

There is little literature concerning the use of intravenous sedation (IVS) techniques in patients with sickle cell disease, although a number of authors have cautioned against it.[13,14] The precipitation of a crisis by emotional stress and anxiety has, however, been reported.[4] An anxious patient with sickle cell disease is therefore vulnerable and, in this situation, the risk of providing sedation may be outweighed by the benefit of anxiolysis.

Patients with sickle cell disease are particularly susceptible to the unwanted effects of respiratory depression which accompany the sedation produced by the administration of intravenous midazolam. Unless a meticulous sedation technique is employed, the hypoxia which can result from such respiratory depression may be sufficient to precipitate a sickle cell crisis, with significant associated morbidity and potentially life-threatening consequences. This group of patients are regarded as an ASA III risk for sedation[15] and, since they will usually have undergone frequent venepuncture for haematological evaluation, intravenous fluid infusion and blood transfusion are likely to be difficult to cannulate. Patients with sickle cell disease should therefore be managed by an experienced sedationist in a specialist centre; they are not considered suitable to receive intravenous sedation in primary care.

In the non-crisis state, most patients with sickle cell disease will have a haemoglobin level of between 5 and 9 g/dl, compared with a normal range for healthy adults of 12–17 g/dl. No minimum haemoglobin level has been recommended for dental patients undergoing IV sedation and most sickle cell patients live and function reasonably well with these low haemoglobin levels. Given that they and their haematologists will be striving for the highest possible haemoglobin level using folic acid, iron supplements, erythropoietin and hydroxyurea, it is unlikely that significant increase prior to sedation without transfusion will be possible. The risks of such a transfusion to facilitate sedation for dental treatment would rarely be considered justified.

The use of 100% oxygen administration for five minutes prior to the induction of general anaesthesia is recommended for patients with sickle cell disease. These patients may also benefit from such pre-oxygenation prior to IV sedation. In addition, supplemental oxygen (2–4 l/min) delivered to the patient via nasal cannulae throughout the procedure and recovery should be considered essential. Midazolam should be carefully titrated and the patient's response and oxygen saturation should be monitored clinically and using oximetry. Table 2 summarizes the management of dental patients with SCD under IV sedation.

- Sedation should be provided by an experienced practitioner in a hospital setting.
- Schedule appointments when the patient is 'well'.
- Administer prophylactic penicillin or clindamycin if bacteraemia is anticipated.
- Give paracetamol 1 g pre-operatively.
- Administer 100% O_2 for 5 minutes prior to induction at 2-4 l/min via nasal cannulae.
- Continue with supplemental O_2 during dental treatment and the recovery period.
- Use 2% lidocaine with 1:80 000 epinephrine as the local anaesthetic of choice.
- Prescribe postoperative antibiotics and analgesia (paracetamol).
- Ensure that adequate nutrition can be maintained and avoid dehydration.
- Treat any postoperative infection promptly and aggressively.

Table 2. Guidance regarding the use of intravenous midazolam sedation for dental patients with sickle cell disease.

Case report 1

A 38-year-old Afro-Caribbean female was referred by her general dental practitioner for the assessment of both maxillary third molars and the mandibular left second molar. She was described as being anxious about any dental treatment. At assessment, the patient complained of painful, broken back teeth. Review of her past medical history revealed sickle cell disease and a number of related conditions, which were managed by haematology colleagues at another hospital. This patient had experienced regular sickle cell crises and frequent hospital admissions (the longest of which exceeded 100 days) prior to the introduction of monthly blood transfusion six years earlier. The patient reported that these transfusions had produced a marked improvement in her general health but such frequent transfusion had resulted in iron overload (transfusion siderosis), which was being treated with deferasirox 3g daily.

Clinical examination revealed fractured restorations in both maxillary third molar teeth and gross caries with pulpal involvement of the mandibular left second molar. Extraction of all three teeth was recommended and the patient consented to have this treatment under local anaesthetic supplemented with intravenous sedation.

Contact was made with the patient's haematologist who agreed to this treatment plan provided that the procedure was undertaken by an experienced sedationist. An early morning

appointment was arranged and it was ensured that the patient was warm and well hydrated before treatment began. It was agreed that supplemental oxygen would be administered throughout the procedure and during recovery, with the use of pulse oximetry to monitor oxygen saturation, which is mandatory. Reassurance was given that the minimum dose of midazolam would be used, with dose titrated against patient response. The procedure was planned for 2 days after the patient's next transfusion.

Cannulation proved to be challenging with multiple attempts being required. A paediatric cannula was ultimately sited on the ventral aspect of the wrist. The patient was pre-oxygenated for 5 minutes prior to the induction of sedation, 2.5 mg midazolam was administered intravenously in increments, after which treatment was accepted by the patient and completed without difficulty. The patient was monitored by the attending dentist and specialist dental nurse during the recovery phase; oxygen saturation throughout the procedure exceeded 96%. When fully recovered, the patient was discharged home in the presence of an appropriate escort.

Case report 2

A 36-year-old black British female was referred by her haematologist for dental care. At that time she was living in a nursing home and had experienced difficulty in finding a local dentist to treat her. In addition to sickle cell disease, she had suffered a stroke in 2005, a fractured hip, rheumatoid arthritis and depression. She was a wheelchair user and was unable to transfer to the dental chair. On examination, she was found to require 5 extractions and multiple restorations. Her oral hygiene was noted to be poor, with deposits of plaque and calculus.

This patient was anxious about dental care but was also worried about the risks of general anaesthesia. Sedation options were discussed and it was decided to perform dental treatment under inhalational sedation (IS) after two appointments with a dental hygienist to improve oral hygiene. Treatment under IS involved the titrated administration of 6l of 50% N_2O: 50% O_2 via a nasal mask. This provided good anxiolysis and, although access was difficult since the patient was treated in her wheelchair using a wheelchair platform (Diaco), both surgical and restorative care was provided. The only changes made to the standard IS administration technique were pre-oxygenation for 5 minutes before sedation and the administration of oxygen for 5 minutes after treatment completion.

Conclusions

Since infection is one of the major risk factors for sickle cell crisis, the prevention of oral disease and infection is vital for this group of patients. There is no contra-indication to the delivery of dental treatment under local anaesthetic, with inhalational sedation if required in the primary care setting, although liaison with the haematologist looking after the patient is advised. The provision of intravenous sedation for patients with SCD should, however, be undertaken in a specialist unit, but can be a safer alternative to general anaesthesia.

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CPD ANSWERS

JULY/AUGUST 2011

1. B, C
2. A, B, C
3. C, D
4. B, C
5. A, D
6. C
7. A, B, C
8. A, B, C
9. A, D
10. A, B, D