

Adult Sickle Cell Disease

A Five-year Experience of Intensive Care Management in a University Hospital in Oman

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فقر الدم المنجلي لدى البالغين تجربة خمس سنوات من العناية المركزة في مستشفى جامعي في عُمان.

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الملخص: فقر الدم المنجلي مرض وراثي ناجم عن نوع غير طبيعي من الهيموغلوبين، وهو واحد من اضطرابات الدم الوراثية الأكثر شيوعاً في منطقة الخليج، بما في ذلك عُمان. قد يحصل مضاعفات تتطلب العلاج في وحدة العناية المركزة. هذه الدراسة تبحث الأسباب التي أدت إلى إدخال المرضى المصابين بفقر الدم المنجلي وحدة العناية المركزة. الطريقة: هذه دراسة استيعابية لجميع المرضى البالغين (12 سنة أو أكثر) المصابين بفقر الدم المنجلي الذين رقدوا في وحدة العناية المركزة بمستشفى جامعة السلطان قابوس بين يناير 2005 وديسمبر 2009. النتائج: تم إحصاء 56 حالة رقدوا في وحدة العناية المركزة. شملت أسباب الرقود متلازمة الصدر الحادة (69.6%)، والأزمات المؤلمة (16.1%)، فشل الأعضاء المتعددة (7.1%) وأسباب أخرى (7.2%). كان معدل وفيات مرضى فقر الدم المنجلي الراقدين في العناية المركزة (16.1%). تم دراسة مستويات الهيموجلوبين والهيموجلوبين-أس حين دخول وحدة العناية المركزة لكن لم تظهر أية دلالة إحصائية معتمدة لهما في فحص (تي) لتوقع الوفاة. تم استخدام نسبة الأرجحية مع فترة الثقة (95%) لدراسة تدابير أخرى داعمة لستة أعضاء للتكهن بالوفيات. كانت الحاجة للحصول على دعم جهاز الدوران والتنفس الميكانيكي مؤشراً جيداً للوفيات، في حين أن الحاجة إلى التنفس غير الغازي وترشيح الدم وعمليات نقل الدم وتبديل الدم لا تعتبر ذات دلالة كبيرة للتكهن باحتمالات الوفاة. الخلاصة: متلازمة الصدر الحادة هي السبب الرئيسي لإدخال مريض فقر الدم المنجلي في وحدة العناية المركزة. خلافاً لغيرها من الإجراءات الداعمة، استخدام الدعم لجهاز الدوران و/أو التنفس الميكانيكي هو مؤشر على ارتفاع معدل وفيات هؤلاء المرضى.

مفتاح الكلمات: فقر الدم، خلية منجلية، متلازمة الصدر الحادة، عُمان.

ABSTRACT: Objectives: Sickle cell disease (SCD) is an inherited disease caused by an abnormal type of haemoglobin. It is one of the most common genetic blood disorders in the Gulf area, including Oman. It may be associated with complications requiring intensive care unit (ICU) admission. This study investigated the causes of ICU admission for SCD patients. **Methods:** This was a retrospective analysis of all adult patients ≥ 12 years old with SCD admitted to Sultan Qaboos University Hospital (SQUH) ICU between 1st January 2005 and 31st December 2009. **Results:** A total number of 49 sickle cell patients were admitted 56 times to ICU. The reasons for admission were acute chest syndrome (69.6%), painful crises (16.1%), multi-organ failure (7.1%) and others (7.2%). The mortality for SCD patients in our ICU was 16.1%. The haemoglobin (Hb) and Hb S levels at time of ICU admission were studied as predictors of mortality and neither showed statistical significance by Student's t-test. The odds ratio, with 95% confidence intervals, was used to study other six organ supportive measures as predictors of mortality. The need for inotropic support and mechanical ventilation was a good predictor of mortality. While the need for non-invasive ventilation, haemofiltration, blood transfusions and exchange transfusions were not significant predictors of mortality. **Conclusion:** Acute chest syndrome is the main cause of ICU admission in SCD patient. Unlike other supportive measures, the use of inotropic support and/or mechanical ventilation is an indicator of high mortality rate SCD patient.

Keywords: Anemia; Sickle cell; Acute chest syndrome; Oman.

ADVANCES IN KNOWLEDGE

- This study gives a descriptive analysis for sickle cell patients admitted to an intensive care unit.
- It validates the rate and causes of sickle cell patients' admission to intensive care unit.
- The need for inotropic support and mechanical ventilation are the main mortality predictors for sickle cell patient in an intensive care unit.

APPLICATION TO PATIENT CARE

- This study will improve sickle cell patient care in intensive care units by understanding causes of admission, complications, length of stay and mortality.
- It helps in realising the modes of organ support required for those patients.

SICKLE CELL DISEASE (SCD) IS AN autosomal recessive disease caused by an abnormal type of haemoglobin, termed haemoglobin S (Hb S). This haemoglobin is caused by the substitution of valine for glutamic acid at the sixth amino acid position of the beta chain.^{1,2} There is more than one form of sickle cell disease resulting from coinheritance of Hb S with other abnormal Hb variants. Sickle cell anaemia (Hb SS) is the commonest form in the USA. Other forms include, Hb S β + -thalassaemia, Hb SD Hb SC. There are rare forms result from coinheritance of other Hb variants such as D-Punjab and O-Arab with Hb S.¹ SCD is much more common in certain ethnic groups and it is considered as one of the most common genetic blood disorders in the Gulf area, including Oman.² In Oman, the incidence of sickle cell disease and sickle cell trait in Omani neonates was 0.3% and 4.8% respectively.³ Although the SCD manifestations *per se* do not typically necessitate critical care management, several life-threatening complications may require intensive care unit (ICU) admission. Some patients have repeated crises, which can result in damage to different organs or systems. The most common complications associated with SCD include vaso-occlusive pain crises (VOC), acute chest syndrome, severe anaemia, infection, cerebral vascular accidents, and multiorgan failure.^{4,5} Because of the fact that there has been little progress in fully understanding the pathophysiology of SCD and finding a cure for it, our management is primarily focusing on treating the negative sequelae and complications of the disease.^{6,7} This study was a descriptive analysis of sickle cell patients who were admitted with complications to the ICU at Sultan Qaboos University Hospital, Oman, over five years and investigated the predictive factors for sickle cell mortality.

Methods

This study was a retrospective analysis of all adult patients ≥ 12 years with SCD admitted to

the SQUH ICU between 1st January 2005 and 31st December 2009. The study was approved by both the institution's Medical Research Committee and its Ethics Committee. SQUH is a tertiary care, teaching hospital with a 12-bed ICU and haematology ward. Data were collected from the SQUH information system (HIS) and its electronic patient records (EPR) as well as the SQUH intensive care database. Information collected included presentation, co-morbidities, organ failure, organ support, length of stay in the ICU, and final outcome. Eight factors were studied as predictors for mortality for SCD in ICU. These included Hb and Hb S levels in addition to six methods of organ support: inotropes, invasive ventilation, non-invasive positive pressure ventilation (NIPPV), haemodialysis/ haemofiltration, blood transfusion and exchange transfusions. The Student's t-test was used for continuous/ordinary variables, while odds ratios (ORs), with 95% confidence intervals (CIs) were used to assess binary variables.

Results

A total of 49 sickle cell patients were admitted 56 times to the ICU; 25 of those admissions (44.6%) were female patients. Two patients had three admissions while three patients had two admissions each. The range of patients' ages was 12 and 52 years, with median of 27 years. Our ICU admits patients ≥ 16 years old, but our protocol allows admission of specific surgical cases and trauma down to the age of 12 years.

Acute chest syndrome was the commonest reason for admission ($n = 39$, 69.6%) [Table 1]. Painful crises were the principal cause of admission for 9 patients (16.1%). However, VOC was present in another 16 cases in association with other major complaints like acute chest syndrome (ACS). Multi-organ failure (MOF) was the cause of admission in 4 patients (7.1%).

Neurological complications related to SCD were found in 2 patients (3.57%). One patient

Table 1: Causes of intensive care unit admission for sickle cell patients.

Cause of admission	Number (N = 56)	Percentage
Acute chest syndrome	39	69.6
Painful crises	9	16.1
Multi-organ failure	4	7.1
Brain insult	2	3.6
Hepatic failure	1	1.8
Surgical cause	1	1.8

was transferred intubated from another hospital with radiological features of cerebral ischaemia and anoxic brain injury. The other patient had a subarachnoid haemorrhage.

One patient was admitted with hepatic failure associated with hepato-renal shutdown and features of hepatic encephalopathy (1.8%). Another 12-year-old patient was admitted to our adult ICU as a surgical case after laparoscopic splenectomy and cholecystectomy with severe intra-operative haemorrhage.

Eight patients were admitted through the Emergency department (14.28%) in comparison to 46 admissions (83.9%) from the ward. Only one patient (1.78%) was referred, intubated, from another hospital directly to our ICU.

The mortality for SCD in our ICU was 16.07% (9 patients), comparable to an ICU-overall mortality of 21.1% during the same period in the same institute. Five cases were admitted with ACS and four cases with MOF.

The length of stay in the ICU ranged from 1 to 23 days. For survivors, the mean lengths of ICU stay was 5 days, while for non-survivors it was 2.7 days. This is considered to be statistically significant ($P = 0.04$).

A total of 27 admissions for those who survived were with those with no co-morbidities (57.4%) in comparison to 4 admissions among those who died (44 %). The survivors' co-morbidities can be classified into: Behcet's disease (1); autoimmune disease (1); hepatitis (C and/or B) virus (5); liver cirrhosis (1); osteoporosis with avascular necrosis of one or more joint (6); glucose-6-phosphate dehydrogenase (G6PD) deficiency (4); nephrotic syndrome (2); asthma (2); chronic renal failure (2), and protein C deficiency with cerebral ischaemia

(1). Four admissions were pregnant patients. It should be taken in consideration that some patients had more than one medical problem or co-morbidity at the time of admission.

Co-morbidities in non-survivors can be classified into: congenital neutropenia (1); dilated cardio-myopathy (1); systemic lupus erythematosus associated with chronic renal failure (2), and nephrotic syndrome (1).

In the ICU, the level of Hb and Hb S at the time of admission was studied as a predictor of mortality. The mean Hb for both, survivors and non-survivors were similar (8.3mg/dl and 8.6mg/dl, respectively). The range of Hb was (4.4–12.5 gm/dl) for those who survived and (6.4–11.2gm/dl) for non survivors. This result is not statistically significant ($P = 0.8$).

For those who survived, the Hb S mean for 36 cases was 63% with standard deviation (SD) 21.5 (11 not available), while for non-survivors the mean Hb S for 7 admissions was 54.5% (2 not available) with SD 25.5. This result is also not statistically significant by t-test ($P = 0.4$). High-performance liquid chromatography (HPLC) was used to study Hb S through Bio-Rad variant II (Bio-Rad Laboratories, Inc., Hercules, California, USA).

Most of the patients in this study were admitted for some time in the ward and received simple or exchange blood transfusions before coming to the ICU.

The odds ratio (OR), with 95% CIs, was used to study the six organ supportive measures as a predictive for the increase in mortality [Table 2]. These supportive measures include the use of inotropes, invasive ventilation, NIPPV, haemodialysis/ haemofiltration, exchange transfusion and top-up blood transfusions.

Requirement for inotropes was a good predictive for mortality (OR 117.3). It means that mortality is much more likely in SCD patient who require cardiovascular support in the form of inotropes. Eight of the 9 patients who died required inotropes. Four of those patients had MOF and another 4 ACS. Three of 47 patients who survived required inotropic support. All the three were admitted with ACS.

Invasive mechanical ventilation (MV) was similarly a good predictive for mortality as 8 of 9 patients who died required MV while another 8 required MV among those who survived (OR 39). Regarding those who required intubation and

Table 2: Types of organ support needed by patients admitted to the intensive care unit.

Organ Support	Survivors	Non-survivors	Odd ratio
Inotropic support	3:44	8:1	117.3
Mechanical ventilation	8:39	8:1	39
Non-invasive ventilation	27:20	1:8	0.09
Blood transfusion	21:26	6:3	1.2
Exchange transfusion	38:9	7:2	0.8
Haemodialysis\ haemofiltration	4:43	4:5	Not Identified

mechanical ventilation among non-survivors, 4 of them had MOF and the other 4 had ACS. Of those who survived, one patient was admitted for subarachnoid haemorrhage, one patient for cerebral ischaemia and anoxic brain injury (ended with tracheostomy), another patient post laparoscopic surgery, and all others with ACS.

NIPPV was studied as a predictor for mortality (OR 0.09). This ratio illustrates that mortality was very unlikely in those patients who have SCD and do require NIPPV. NIPPV was required in 28 admissions (27 survived). The only patient who died was a case of ACS who had a sudden cardiac arrest while he was on NIPPV.

Simple blood transfusion was used to support 35 SCD admissions in ICU (62.5%). A total of 29 of them survived while 6 died. The need for blood transfusion was not considered as a very good predictor for mortality (OR 1.2). Blood exchange transfusion was used in 45 admissions (80.4%), 7 of them died. The need for exchange transfusion does not predict mortality (OR 0.8).

Continuous veno-venous haemodialysis (CVVHD) was used in 8 admissions; four of them died (OR 8.6). Two of those who died were admitted because of ACS as a part of generalised VOC and they developed acute renal failure. The other two were admitted with systemic lupus erythmatosus and chronic renal failure. For the 4 admissions that had acute renal failure and survived, 3 had ACS and one had hepato-renal shutdown.

As haemodialysis was used for both acute and chronic renal failure, it was not considered a good indicator of severe acute illness and mortality

Discussion

Sickle cell vaso-occlusion may involve both the micro- and macrovasculature. It is the most important pathophysiologic event in SCD and explains most of its clinical manifestation. The median age at death in patient with SCD is 42 years for males and 48 years for females.⁸

Acute chest syndrome (ACS) is a common cause of admission and death among patients with sickle cell disease. ACS is usually caused by infection, pulmonary infarction or fat embolism. Painful crisis is the main cause of admission in those patients (90%). To reach a diagnosis of ACS, we need a triad of fever, respiratory distress and new interstitial infiltrates on chest X-ray.^{9,10,11}

This study represents the first data collection and analysis of sickle cell patients admitted to an ICU in Oman. In SQUH, the adult 12 bed ICU admits both medical and surgical cases including trauma patients. We admit some of those patients who require non-invasive ventilation (NIV) as well because our high dependency units (HDU) setting is not completed. We also sometimes accept paediatric trauma or post surgical patients ≥ 12 years for specific reasons. Over five years there were 56 SCD admissions which represent 3.5% of total admissions in our ICU. We referred to our patients as sickle cell disease patients depending on their high Hb S level, although genotyping studies are required for all patients to confirm the Hb SS or other sickle cell types of Hb. A retrospective study in the UK reported that Hb SS was found in 84% of their ICU admission while the other 16% was Hb SC.¹² This might possibly refer to the severity of disease expression in patients having this type of haemoglobin. All sickle cell patients' admissions, except one, were for medical reasons. Two patients had 3 repeated admissions while three patients had 2 admissions each. These repeated admissions were divided between ACS and painful crisis. No mortality was reported among those who had repeated admissions.

It was sometimes difficult to choose a single reason for admission as some patients may have a complex clinical presentation with more than one complaint and more than one organ involved. This complexity may be related to the nature of SCD and the sickling process. ACS was the most common cause of admission (69.6% in our ICU) compared to

Table 3: Clinical data for non-survivors among sickle cell patients admitted to intensive care unit (ICU)

Age(years)/ Gender	Admission Hb gm/dl	Admission Haemoglobin S %	Co-morbidities	Days of ICU stay	Cause of Admission	Types of Support
19/M	8.8	48.4	Nil	2	Sepsis, MOF	I, V, B, E
28/F	8.7	36.2	Nil	8	ACS, MOF	I,V,B, H
19/M	9.6	NA	SLE, CRF, Congenital neutropenia	1	ACS/PE?	I,V, E
22/F	7.2	36.5	SLE, CRF	2	Sepsis, MOF	I, V, B, E, H
31/F	6.4	NA	SLE, nephrotic syndrome	1	ACS, sepsis	I, V, B, E
53/F	7.9	33.2	Nephrotic syndrome.	3	ACS/PE?	I, V, B, H
19/F	7.7	91.9	Nil	3	ACS, sepsis	I, V, B, E, H
28/F	9.9	77.8	Nil	1	ACS	NIV, E
30/M	11.2	89.6	Dilated cardiomyopathy	1	ACS, MOF	I, V, E

Legend: M = male; F = female; MOF = multi organ failure; I = inotropes; V = mechanical ventilation; B = blood transfusion; E = exchange transfusion; ACS = acute chest syndrome; H = haemodialysis; SLE = systemic lupus erythematosus; CRF = chronic renal failure; PE = pulmonary embolism; Nil = no co-morbidities, NIV = non-invasive ventilation.

30% in Gardner's study.¹² All those patients required ventilatory support whether it was invasive or non-invasive. In our study, MOF (4 patients) was the third cause of admission after painful crisis with a rate of 7.1%, compared to 17% in Gardner's study.¹²

The mortality rate for sickle cell patients in our study was less than the overall mortality in our ICU (16.1% versus 21.1%). Gardner *et al.* reported a higher ICU sickle cell patient mortality compared to overall ICU mortality in the same period and same institute (19.6% versus 17.6%).¹² We can explain this difference by the cases of painful crises (9 admissions) in our study in which no death was reported, while in the British study there were no painful crises as a cause of admission. In fact, cases of painful crisis can be treated in the ward or in HDU if no other organ support measures are required. According to our hospital protocol, patients who require ICU admission are those on very high doses of opioid infusion with no response, those with compromised cardiovascular or respiratory functions, and those who require additional ketamine infusion. We agree that if there is a well-structured HDU, admission of those cases to an ICU can be avoided.

Two main causes of death in ICU sickle cell patients were found in our study [Table 3]: ACS (5 patients, 55.6%) and MOF (4 patients, 44.4%). Three of those ACS patients stayed for less than one day and one patient died after 3 days after admission. Regarding the four MOF patients who died, two deaths were triggered by ACS while another two

were associated with sepsis.

Gardner *et al.* found that MOF and stroke (haemorrhage/ischaemia) were the main causes of death in sickle cell patients in their ICU, 33.3% for each condition. ACS was next commonest cause with a rate of 22.2% while trauma caused death in 11.1% of cases.¹² A review of the causes of death in adult patients (age >20 years) with sickle-cell disease in Jamaica by Thomas *et al.* showed that ACS was responsible for 22% of death in those patients. Other common causes of death in Jamaican sickle cell patients were renal failure 15.7%, pregnancy-related problems 7.4% and sepsis 3.7%.¹³

The length of stay in the ICU ranged from 1 to 23 days. For non-survivors, 4 of 9 patients (44%) stayed for less than 24 hours. One patient with a history of dilated cardiomyopathy was admitted from the Emergency department with MOF. The other 3 patients were admitted from the ward with VOC/ACS and suddenly deteriorated. One of them had clinical and echocardiographic features suggestive of pulmonary embolism (no spiral computed tomography [CT]). The other two had an element of sepsis in addition to ACS. This result can be referred to the nature and complexity of the disease with possibility of rapid deterioration in some cases. The other explanation may be the possibility of delay of ICU admission to give intensive supportive measures especially for patient with features of sepsis.

The majority of the cases (83.9%) had been

admitted to the ward for some time before being moved to our ICU. Those patients received all necessary supportive measures in the ward including blood transfusion and exchange transfusion depending on their length of stay. This may mask the role of Hb and Hb S level at the time of ICU admission as an indicator for severity of the crises or even mortality. However, simple and exchange transfusions were performed as supportive measures in 62.5% and 80.4% of ICU admissions respectively depending on base line Hb and Hb S levels and the patient's general condition.

The main aim of red blood cell (RBC) transfusion in SCD is to prevent and resolve vaso-occlusive events that result in ACS, stroke, and other ischaemic organ damages. This transfusion can be chronic or intermittent. The effect of RBC transfusion is improving the oxygen-carrying capacity; lowering blood viscosity; diluting the concentration of Hb S, and suppressing production of sickle RBCs due to the improvement in tissue oxygenation.^{14,15} The indications for intermittent RBC transfusion include: acute symptomatic anaemia; sequestration crisis; aplastic crisis; acute stroke; ACS; sepsis; acute multiorgan failure, and preparation for general anesthesia or ophthalmic surgeries.¹⁴ Simple transfusion is more convenient and easier than exchange transfusion and it is more frequently used for acute transfusion, but exchange transfusion is a good option in an acute crisis patient with a higher pretransfusion Hb level or when volume overload and hyperviscosity are of particular concern.¹⁶

One of the therapeutic aims of exchange transfusion in vaso-occlusive event like ACS is to decrease the proportion of erythrocytes containing Hb S to less than 30%, thereby improving microvascular perfusion. Two volumes of red cell exchange transfusion decrease HbS containing red blood cells to less than 20%. However, a reduction in Hb S levels may not be the only explanation for the early and dramatic clinical improvement often demonstrated in patients with ACS after exchange transfusion. This is because neutrophils and platelets, which are inflammation markers, may contribute to venous stasis in the pulmonary microcirculation.^{14,15} Alhashimi D *et al.*, during their Cochrane review, found that there is no reliable evidence to support or refute the effectiveness of simple or exchange blood transfusions in treating

ACS.¹⁷

Inotropic support was required in 88.9% of those who did not survive in comparison to 6.4% in survivors. It is clear that this difference is basically related to the seriousness of the clinical condition and the presence of elements of sepsis and MOF in most of non-survivors. The same facts can be applied to invasive ventilation as it was required in 88.9% in non-survivors compared with 17% for those who survived. Patients who required one or both of these organ supports have a significant higher risk of mortality. By contrast, non-invasive ventilation (NIV) does not carry that risk as it is usually used for more stable patients with ACS who require some ventilatory support.

ACS may be triggered in SCD by infection. Usually the clinical presentation is similar whether it is due to infectious or non-infectious causes. Therefore, antibiotics can be considered as one of the supportive measures for those patients. Antibiotic cover as a line of treatment for those patients was not included in detail in our study.¹⁸

Finally, there are some limitations to this retrospective study. The sample size was not large; this might be overcome in future research by including multicentre data. The other point was the difficulty in assessing the direct effect of the co-morbidities on mortality. The third point was related to our hospital ICU protocol, which led to admitting some categories of sickle cell patients who would normally be treated in an HDU rather than an ICU.

Conclusion

SCD is a common haematological problem in Oman. ACS was the main reason for ICU admissions in our study. The mortality for SCD was slightly less than the overall ICU mortality during the same period. The need for inotropes and invasive ventilation were considered the main predictors of mortality. On the other hand, the need for non-invasive ventilation, haemofiltration, blood transfusions and exchange transfusions were not significant predictors of mortality.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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