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Original Article

Outcome of cranial surgery in Nigerian patients with hemoglobinopathies: A retrospective study

Oluwakemi A. Badejo, Olusola K. Idowu[1], James A. Balogun, Wuraola A. Shokunbi[2], Simbo D. Amanor-Boadu[1], Matthew T. Shokunbi

Departments of Surgery, [1]Anaesthesia and [2]Haematology, College of Medicine, University of Ibadan, Ibadan, Nigeria

E-mail: Oluwakemi A. Badejo - kemibadejo@yahoo.com; Olusola K. Idowu - zolaspecky@yahoo.com; James A. Balogun - jamesbalogun@gmail.com; Wuraola A. Shokunbi - wuraolashokunbi@yahoo.co.uk; Simbo D. Amanor-Boadu - sim7652@yahoo.co.uk; *Matthew T. Shokunbi - temitayoshokunbi@yahoo.com
*Corresponding author

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Abstract

Background: Surgical intervention in patients with hemoglobinopathies has been extensively reviewed in the literature, but information on the outcome of cranial surgery in this patient population in sub-Saharan Africa is limited.

Methods: This is a retrospective study of patients with hemoglobinopathies, who underwent brain surgery in our facility. The review covered a 5-year period. We examined patient- and surgery-related variables and described the surgical complications as well as the 60-day mortality.

Results: A total of nine procedures (eight under general anesthesia and one under local anesthesia) were performed on seven patients with hemoglobinopathy during the study period. Eight (88.9%) of these were done in female patients and one (11.1%) in a male patient. Six (66.7%) were performed in patients with no previous history of blood transfusion. Hb SC accounted for five (55.6%), Hb SS for three (33.3%), and Hb CC for one (11.1%) procedure, respectively. Three (33.3%) of these procedures were brain tumor-related, three (33.3%) trauma-related, one (11.1%) cosmetic, one (11.1%) vascular, and one for a postoperative complication. Only one (11.1%) procedure was associated with preoperative blood transfusion, whereas there was a need for blood transfusion following five (55.6%) of the procedures. There was a mortality rate of 11.1% (1 case). Other complications were recorded after three (33.3%) of the procedures and none with five (55.6%) of the procedures.

Conclusion: Neurosurgery is possible and safe in patients with hemoglobin disorders. Adequate preoperative preparation, proper anesthetic techniques, meticulous surgery, and excellent postoperative care can help optimize outcome of surgical intervention in this patient population.

Key Words: Blood transfusion, hemoglobinopathy, neurosurgery, sickle cell disease

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INTRODUCTION

Hemoglobinopathies are autosomal recessive hematological genetic disorders characterized by production of abnormal hemoglobin. These include structural defects of the beta globin chain (hemoglobin variants) and quantitative abnormalities of alpha or beta-globin chains (thalassemia syndromes).[12,18] Hb S (the sickle hemoglobin) occurs when valine replaces glutamic acid at the sixth position of the beta-globin gene, whereas Hb C results from substitution of glutamic acid with lysine at this same position.[5,23] Over 1000 hemoglobin variants exist, of which Hb S is the commonest in sub-Saharan Africa.[12,28] The most prevalent form of hemoglobinopathy, sickle cell disease, develops from homozygosity of the Hb S genetic mutation (Hb SS; sickle cell anemia) or from pairing of the Hb S gene with a different type of Hb variant.[28] Hb SC, Hb S beta-thalassemia, and Hb SD are a few other examples of hemoglobin disorders besides Hb SS. Individuals with hemoglobinopathy have abnormal red blood cells, which tend to "sickle" under hypoxic conditions. Repetitive sickling of these erythrocytes culminates in recurrent vaso-occlusive episodes, hemolysis, chronic anemia, and end-organ infarction, which are the hallmarks of the disease.[12,27] Homozygous hemoglobin C disease is a relatively benign form of hemoglobinopathy, which manifests with mild hemolytic anemia, splenomegaly, and abnormalities of the erythrocytes on blood smear (mostly targets cells or microspherocytes but rarely intra-erythrocyte crystal inclusions).[5] About 5–7% of the total world's population have been estimated to be carriers of disorders of hemoglobin. Sub-Saharan Africa has the highest global prevalence, of which Nigeria carries the greatest disease burden.[1] Advances in knowledge and management of this condition have resulted in significant improvement in the quality of life and longevity of affected persons.

This group of patients may require surgical intervention during the course of their lifetime, either as a direct consequence of their disease or from unrelated causes. The surgical management of patients with sickle cell disease poses a daunting challenge because of a variety of factors. These include low blood reserve, reduced oxygen-carrying capacity of the abnormal red blood cells under anesthesia, increased susceptibility to infections, the high tendency for thromboembolic events, and the potential for precipitating sickle cell crisis.[3] However, proper preoperative preparation and meticulous intra/postoperative care have significantly improved surgical outcome.[16] Although data exist on surgical outcomes in patients with hemoglobinopathy in the literature, there is a dearth of information regarding the results of neurosurgical procedures in these patients, especially in sub-Saharan Africa. We report the outcome of brain surgery in a cohort of Nigerian patients with hemoglobinopathy in our facility over a 5-year period.

METHODS

We performed a retrospective review of all patients with hemoglobinopathy, who underwent cranial neurosurgical procedures in our facility between January 1, 2013 and January 1, 2018. Data extracted from their medical records include their biodata, type of hemoglobinopathy, history of previous surgeries, comorbidities, past blood transfusion, previous sickle cell crisis, and form. Compliance with routine medications, neurosurgical diagnosis, steady-state packed cell volume, type of anesthesia, and neurosurgical procedure done were recorded. We also documented the estimated intraoperative blood loss, pre/postoperative packed cell volume, intra/postoperative blood transfusion, duration of surgery, the period of intensive care unit admission if any, length of hospitalization, complications, and outcome. These were all recorded and analyzed. The primary outcome measure was the 60-day mortality, and the secondary outcome measures were the procedure-related complications.

RESULTS

We performed 1245 neurosurgical procedures during the study period. There were seven patients with hemoglobin disorders, who had nine (0.72%) procedures during this period. Table 1 shows the demographic and clinical characteristics of the seven patients. One patient had a cranioplasty 16 months after a wound debridement and elevation of an infected compound depressed right frontal fracture and another patient had reopening craniotomy and evacuation of a right temporoparietal acute extradural hematoma 2 days following clipping of a basilar tip aneurysm. One male patient accounted for one (11.1%) procedure, whereas six female patients accounted for eight (88.9%) procedures. Hb SC predominated the series, occurring in four patients who underwent five (55.6%) procedures, followed by Hb SS found in three (33.3%) procedures carried out on two patients and Hb CC in a single (11.1%) procedure. The age range was 4–70 years. Only one (11.1%) procedure was done under local anesthesia, whereas the rest of the procedures (88.9%) were performed under general anesthesia with endotracheal intubation. About 33.3% of the surgeries were brain tumor-related; two (22.2%) for pituitary tumors, and one (11.1%) for a right temporal glioma [Figure 1]. Three other procedures (33.3%) were for trauma-related pathologies (Figure 2 represents one of the cases), and one (11.1%) procedure each for cranioplasty, aneurysm clipping, and postoperative extradural hematoma evacuation, respectively. The steady-state packed cell volume ranged from 18% to 33% in five of the patients who underwent six procedures

Table 1: Demographic and clinical characteristics of patients with hemoglobinopathies undergoing cranial surgery

Age (years)	Sex	Diagnosis	Procedure	Anesthesia	Hemglobin phenotype	Previous blood transfusion	Outcome	Duration of follow-up
55	M	Chronic subdural hematoma	Burr-hole drainage	GA	SC	Yes	Good	60 months
48	F	Sellar/Suprasellar tumor	Craniotomy and tumor excision	GA	SS	Yes	Good	18 months
4	F	Open depressed right frontal fracture	Wound debridement and elevation of depressed skull fracture	GA	SC	No	Good	27 months
26	F	Basilar tip aneurysm	Craniotomy and clipping of aneurysm	GA	SS	Yes	Good	27 months
26	F	Postoperative extradural hematoma	Reopening craniotomy and evacuation of extradural clot	GA	SS	Yes	Good	27 months
70	F	Chronic subdural hematoma	Burr-hole drainage	LA	CC	Yes	Good	19 months
50	F	Sellar/Suprasellar tumor	Endoscopic endonasal transsphenoidal resection	GA	SC	No	Died	6 days
5	F	Right frontal bony defect	Cranioplasty	GA	SC	Yes	Good	12 months
52	F	Right temporal glioma	Craniotomy and tumor excision	GA	SC	No	Good	2 months

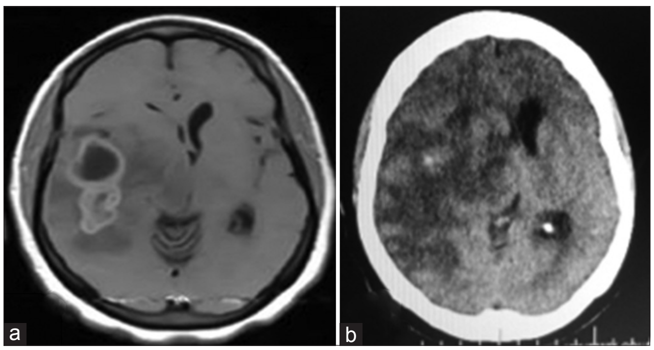

Figure 1: Right temporal tumor: axial cranial images. (a) Preoperative: cranial magnetic resonance imaging (T1, contrast-enhanced) showing lobulated, partly cystic tumor. Histologically diagnosed as anaplastic astrocytoma. (b) Postoperative: cranial computerized tomography scan (contrast-enhanced); gross near-total resection

(not known in the others), with the lowest recorded values in patients with the Hb SS variant [Table 2]. The pre- and postoperative packed cell volume ranged from 18–36% and 16–34%, respectively [Table 2]. Estimated intraoperative blood loss ranged between 40 and 1500 ml. Only one of the patients had a preoperative blood transfusion, necessitated by intracranial bleeding, complicating an initial procedure (clipping of a basilar tip aneurysm) 2 days earlier [Table 2]. There was the need for transfusion of at least 500 ml of whole blood during five (55.6%) of the procedures, whereas there was no blood transfusion requirement during or after the rest of the procedures. Six of the patients had comorbidities, which accounted for eight (88.9%) procedures. The comorbidities included steroid-induced hyperglycemia, hypertension, diabetes mellitus, chronic osteomyelitis, hepatitis B infection, sepsis, and a chronic leg ulcer. All of the patients had experienced vaso-occlusive crisis in the past, whereas one patient who underwent two procedures (22.2%) had a history of hemolytic crisis as well. There were no postoperative complications in five (55.6%), whereas the postoperative

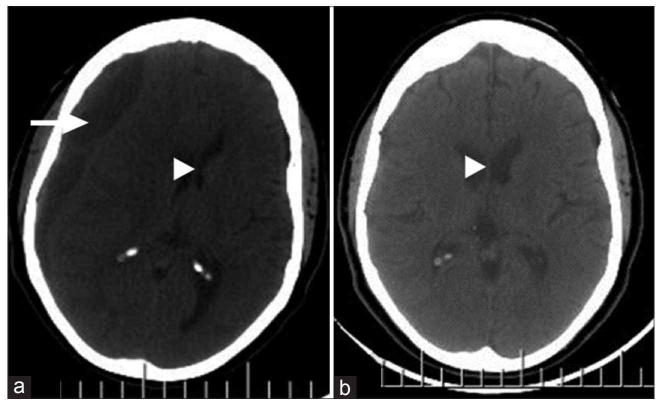

Figure 2: Right cerebral hemispheric chronic subdural hematoma; axial images, cranial computerized tomography scan. (a) Preoperative: mixed hypo- and isodense subdural collection (white arrow) with substantial mass effect (white arrow head). (b) Postoperative (6 weeks later): total evacuation of hematoma and restoration of brain midline (white arrow head)

complications recorded following three (33.3%) of the procedures, included anaphylactoid reaction, operation site extradural hematoma, and a vaso-occlusive crisis. These were successfully managed in all instances. There was a mortality rate of 11.1% following one procedure (11.1%). A previous history of blood transfusion and surgery were obtained in six (66.7%) of the procedures. Four of the patients who underwent five (55.6%) procedures were admitted into the intensive care unit following surgical intervention, the duration of which ranged between 1 and 5 days. Only one patient, representing one procedure (11.1%), required mechanical ventilation. The duration of hospitalization postoperatively was between 5 and 34 days.

DISCUSSION

Hemoglobinopathy remains a disease of global health importance.[2] Although prevalent in regions of high

Table 2: Preoperative hematological parameters and blood transfusion requirement of the patients

Steady-state PCV (%)	Preoperative PCV (%)	Preoperative blood transfusion (ml)	Intraoperative blood loss (ml)	Intraoperative blood transfusion (ml)	Postoperative blood transfusion (ml)	Postoperative PCV (%)
Unknown	33	Nil	100	Nil	Nil	29
18	18	Nil	400	1000	500	16
Unknown	33	Nil	320	50	300	32
21-25	36	Nil	1100	1000	500	25
21-25	25	1500	300	Nil	Nil	29
30-33	26.8	Nil	150	Nil	Nil	27
30	35	Nil	1500	1500	Nil	34
Unknown	30	Nil	40	Nil	Nil	26
28-30	31	Nil	350	500	Nil	32

M: Male; F: Female; GA: General anesthesia; LA: Local anesthesia; PCV: Packed cell volume; ml: milliliters

malaria endemicity like sub-Saharan Africa, Asia, India, Brazil, the Middle East, Caribbean, and the East Mediterranean region, by reason of migration and slave trade, it is beginning to spread beyond these communities to regions with naturally lower occurrence such as Europe and America.[2,13,24,30] About 5–7% of the global population have been estimated to be carriers of disorders of hemoglobin (mostly sickle cell disease) with >70% of this disease burden being borne by sub-Saharan Africa and the highest prevalence occurring in Nigeria, where the carrier and newborn rates are 6–30% and 2%, respectively.[1,9,21] Indeed, of the over 300,000 annual new births with hemoglobinopathy worldwide, more than 150,000 occur in Nigeria.[2,13,21] Although premarital counseling and genetic screening, measures with the potential to reduce its incidence, have been widely utilized in different regions of the world, it continues to be a significant cause of morbidity and mortality in sub-Saharan Africa and notably, Nigeria.[20] According to the World Health Organization, the under-5 mortality rate from hemoglobin disorders is about 3.4% worldwide and 6.4% in Africa.[21] However, advances in knowledge and understanding of the disease have improved the longevity of affected patients as well as their quality of life.[25,31] Significant causes of morbidity and mortality in sickle cell disease have been studied extensively over time and measures implemented to modify the disease severity. The latter includes counseling, screening of newborns, long-term blood transfusion, hydroxyurea therapy, transcranial Doppler (to screen for patients at risk of ischemic stroke), stem cell therapy, antibiotic prophylaxis, and *Haemophilus influenza* vaccination.[14,25,31] Patients with sickle cell disease have a higher risk of having surgery than those without the disease and at an earlier age, on account of increased susceptibility to developing conditions like cholelithiasis, avascular necrosis of the neck of the femur, osteomyelitis, and chronic leg ulcer.[10] Neurosurgical disorders reported in sickle cell patients in the literature include but are not limited to spontaneous epidural hematoma, anaplastic ependymoma, salmonella epidural abscess, moyamoya disease, salmonella enteritis brain abscess, intracranial aneurysms, and vertebral osteomyelitis with epidural abscess.[4,7,8,15,17,22,26] Our study covered a broad spectrum of neurosurgical disorders ranging from trauma, neoplastic, vascular to cosmetic. The high female preponderance in our study is likely attributable to the more prolonged survival of females with sickle cell disease compared to males.[19] The most frequent hemoglobin phenotype in our series was SC rather than Hb SS as seen in the general population.[14] This disparity may be a reflection of the longer survival in Hb SC compared to Hb SS and also because the only pediatric patient in this group presented for two procedures.

Great care must be taken to avoid factors that can predispose patients to sickle cell crisis in the preoperative period. These include hypoxia, acidosis, and hypothermia.[16] The preoperative practice in some institutions includes prevention of hypoxia and dehydration and preoperative blood transfusion in elective patients to reduce the overall percentage of sickled cells and thus the risk of sickle cell-related crises.[6,11] A Cochrane meta-analysis in 2016 demonstrated very low-quality evidence that preoperative blood transfusion may prevent the development of acute chest syndrome but none to suggest prevention of other complications. There was no difference in mortality between those who had a preoperative blood transfusion and those who did not. Similarly, aggressive blood transfusion (to reduce the percentage of sickled cells) was not superior to conservative blood transfusion (to correct anemia) in preventing vaso-occlusive crisis, acute chest syndrome, any blood transfusion-related complication, any perioperative period complication, or severe infection.[10] In our series, only one procedure (11.1%) was associated with preoperative blood transfusion. This patient had craniotomy for a basilar tip aneurysm 2 days earlier, during which there was a substantial intraoperative blood loss (1100 ml) and hemodynamic instability, which necessitated blood transfusion. She developed postoperative extradural hematoma, on account of which she was re-operated.

Based on our experience with our patients, we suggest that preoperative workup of patients with sickle cell disease includes complete blood count, serum electrolytes, coagulation profile, and adequate hydration (to prevent vaso-occlusive crisis). Preoperative blood transfusion should be reserved for patients with hematocrits below their known steady-state levels or less than 30% in those whose steady-state levels are unknown. These patients should have preoxygenation to 100% prior to commencement of induction of anesthesia and adequate oxygenation must be maintained throughout the surgery. Intraoperative measures should include blood transfusion if blood loss exceeds 500 ml or if there is evidence of hemodynamic instability. It is important to prevent hypothermia and achieve optimal pain control in these patients to forestall sickle cell disease-related crises. Given the hypercoagulable states of these patients and the increased risk of thromboembolism, we advocate institution of nonpharmacologic deep venous thrombosis prophylaxis techniques and early ambulation when not contraindicated. Prophylactic administration of broad spectrum intravenous antibiotics and (intravenous) antibiotics coverage continued up to 48 h after surgery should be employed to prevent postoperative sepsis.

Various publications have shed light on the surgical outcomes in patients with sickle cell disease, with most of these involving orthopedic, general surgical, and otorhinolaryngological procedures.[16,29] However, there is a paucity of information on the outcome of brain surgery in sickle cell disease patients, especially in sub-Saharan Africa. Koshy *et al.* noted in their series that non-sickle cell disease-related postoperative complications occurred less frequently following general anesthesia compared to local and regional anesthesia. They also observed that sickle cell disease-related postoperative complications were higher in Hb SS patients who undergo regional anesthesia compared with general and local anesthesia.[16] In a series of orthopedic surgery in patients with sickle cell disease, the "serious" complication rate was 67%. This included excessive blood loss, sickle cell crisis, and blood transfusion complications.[29] The mortality rate in the same study was 1.4%.[29] Morbidity (33.3%) and mortality (11.1%) rates in our series were higher compared to those of previous outcome studies of Koshy *et al.*, Coker *et al.*, and Hankinson *et al.*[6,15,16] It should be noted that in some of these studies, the patient populations were dissimilar to ours with respect to the type of procedure done and (procedure-associated) risk level.

All the nondeath complications in our patients were successfully managed. Only one patient in our series had postoperative sepsis, which was related to a preoperative infected, plated, and malunited right femoral fracture. He subsequently had implant removal and modified Belfast procedure by the orthopedic team. The presence of comorbidities did not reflect negatively on the outcome in our series. One of the patients had vaso-occlusive crisis following debridement and elevation of an open depressed right frontal fracture, which was secondary to preoperative sepsis. She in fact had a vaso-occlusive crisis in the immediate preoperative period. The mortality was in a 50-year-old Hb SC patient, with a giant pituitary tumor who had an endoscopic transsphenoidal resection, which was terminated on account of excessive intraoperative blood loss (1500 ml). She was transfused with three units of whole blood and a unit of fresh frozen plasma. The patient's preoperative and postoperative packed cell volumes were 34% and 35%, respectively. She had transient diabetes insipidus postoperatively but remained neurologically intact. The patient had a sudden neurologic deterioration 17 h later, with no intracranial complication on cranial computerized tomography scan. This necessitated endotracheal intubation and mechanical ventilation. The neurologic status worsened progressively, and she died on the fifth-day postoperation. An autopsy revealed residual pituitary tumor, lobar pneumonia, benign nephrosclerosis, hepatomegaly, fatty liver, and splenomegaly (with acute congestion). Could the hemorrhagic complication have been caused by sickle cell hepatopathy or was it purely a surgical complication? The mortality may be as much related to the procedure as it was to the patient's sickle cell disease. The only other type of hemoglobinopathy in our study aside sickle cell disease was Hb CC, which constituted 0.08% of all cases done over the study period. At follow-up, which ranged between 2 months and 5 years, six of the patients representing eight (88.9%) of the procedures were alive and well.

CONCLUSION

Neurosurgery is possible and safe in patients with hemoglobin disorders. Proper preoperative preparation, meticulous anesthesia/surgery, and excellent postoperation care can help improve outcome.

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Conflicts of interest
There are no conflicts of interest.

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