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Surgical and medical perioperative management of sickle cell retinopathy: A literature review

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Abstract

The most common ophthalmic manifestation of sickle cell disease (SCD) is sickle cell retinopathy (SCR), which can lead to loss of vision due to complications of proliferative sickle retinopathy (PSR). Eventually, vitreoretinal surgery may be indicated in these patients to help preserve or improve vision. Unfortunately, SCD can cause systemic and ophthalmic vaso-occlusive and ischemic complications, which necessitates adequate perioperative planning in these patients undergoing surgery. The purpose of this review was to appraise studies of patients with PSR undergoing vitreoretinal surgery to identify the common medical and surgical perioperative measures employed in these cases. The full-texts of 11 original studies published between 1973 and 2018 were reviewed. Over the last 16 years, 7 studies of 108 eyes undergoing posterior segment surgery for vitreoretinal complications of PSR did not report any ischemic complications related to SCD. It is likely that modern surgical techniques dramatically reduced the risk of these complications. Perioperatively, most studies avoided retrobulbar anesthesia and the use of epinephrine, and the use of exchange transfusions is seemingly not required prophylactically in these patients undergoing vitreoretinal surgery. Customized perioperative planning may be required in complex cases, and these patients should be identified and treated through collaboration between ophthalmic surgeons and hematology specialists.

Introduction

Sickle hemoglobin results from a mutation that leads to the substitution of glutamic acid to valine (HbS) or glutamic acid to lysine (HbC) at position 6 of the beta globin chain.^{1,2} One of numerous β -thalassemia mutations have also been described in patients with HbS.³ Under conditions of hypoxia, acidosis, oxidative stress and infection, this defective hemoglobin takes on the conformation of a sickle or crescent. The sickle hemoglobin is less flexible, more prone to hemolysis and leads to various manifestations of anemia and vaso-occlusive events.⁴ Sickle cell disease (SCD) is an autosomal recessive condition in which individuals inherit an abnormal sickle hemoglobin variant from each parent. In the United States,

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roughly 100,000 individuals have SCD, with most affected individuals being of African ancestry or less commonly, of Hispanic, Middle Eastern or Asian Indian descent.^{5,6}

Patients with SCD can suffer from a number of systemic acute or chronic complications due to vaso-occlusive crises and chronic anemia including avascular necrosis, lower limb ulceration, priapism, cerebrovascular disease, myocardial infarction, cardiomyopathy, renal and hepatic disease and pulmonary disease.⁷ From an ophthalmologic standpoint, SCD can lead to orbital bone infarction or orbital hematoma,⁸ ischemic optic neuropathy,⁹ hyphema,¹⁰ retinal artery occlusion¹¹ and sickle cell maculopathy.¹² The most common ophthalmic manifestation of SCD is sickle cell retinopathy (SCR), which can be non-proliferative (NPSR) or proliferative (PSR).¹³ Typically, NPSR involves lesions in the peripheral retina that do not lead to vision loss.¹⁴ PSR involves “sea-fan” neovascularization and autoinfarction, vitreous hemorrhage (VH), and in more severe cases, fibrovascular proliferation leading to tractional retinal detachment RD).^{15,16} Surgery for PSR may be indicated in cases of nonclearing VH and/or RD.¹⁶⁻¹⁸

Historically, scleral buckling surgery with cryotherapy was the mainstay of treatment for sickle-related RDs.^{19,20} Unfortunately, a devastating complication known as anterior segment ischemia (ASI) has been reported to be more common in patients with SCR. This revealed the propensity of patients with SCR to have complications related to stress-induced vaso-occlusion and ischemia.^{21,22} Therefore, SCR patients undergoing vitreoretinal surgery require careful planning and customized perioperative management to prevent these intra- and postoperative difficulties even in the current era of small-gauge vitrectomy.^{17,23,24} The medical and surgical perioperative management of patients with SCR undergoing vitreoretinal surgery has not been well-described.^{5,24} Therefore, the purpose of this review was to evaluate studies of patients with PSR undergoing vitreoretinal surgery and identify common perioperative measures undertaken to prevent ischemic complications related to SCD. The role of laser photocoagulation is also discussed.

Literature Review

Ovid Medline and PubMed were searched from inception through November 1, 2018 for studies reporting on outcomes of patients with SCR undergoing vitreoretinal surgery. All primary research studies, including case reports, retrospective and prospective cohort studies were included in this review. Table 1 outlines and summarizes the identified studies whose full-texts were retrievable.

The full-texts of 11 original studies published between 1973 and 2018 were reviewed. Although not included in Table 1, the first report of ASI occurring in patients with PSR undergoing scleral buckling (SB) procedures for RD was published by Ryan and Goldberg in 1971, prior to the vitrectomy era.²² In their study, they reported a high rate of ASI (71%), and postulated that the encircling procedure in conjunction with surgically induced inflammation and laser retinopexy compromised circulation in the ciliary vessels enough to induce sickling and ischemia. Therefore, they recommended preoperative exchange transfusion, the avoidance of sympathomimetic agents, supplemental oxygen, avoidance of treatment or pressure on the ciliary vessels, and extraocular muscle removal.²² Soon after

this, Freilich and Seelenfreund (1973) reported the successful treatment of PSR in three patients via SB procedures in a hyperbaric chamber.²⁵ However, these methods were not replicated by other authors.

Another case of ASI was reported by Jampol et al. (1982) in their report of 19 eyes undergoing posterior segment surgery for PSR complicated by RD or VH.²⁶ Their cases of RD were successfully treated by SB and patients with VH were treated adequately via pars plana vitrectomy (PPV). However, only 50% of eyes undergoing PPV with SB for tractional RD had improved vision. Most of their cases (14/19) received exchange transfusions with a goal to achieve hemoglobin A (HbA) levels between 40-60%. Other perioperative measures included supplemental oxygen delivery perioperatively, the avoidance of sympathomimetic agents in analgesic and topical preparations, and careful intraocular pressure monitoring. Among the five eyes that did not receive exchange transfusions, one developed ASI. The same eye was also noted to have received epinephrine in the retrobulbar anesthetic. This study therefore identified four possible risk factors for ASI: (1) the lack of exchange transfusion, (2) the retrobulbar route of analgesic administration, (3) the administration of epinephrine in the anesthetic preparation, and (4) the use of a scleral buckle.²⁶

The necessity of the use of preoperative exchange transfusions was later challenged by Pulido et al. (1988).²⁷ In their study of 11 eyes of patients surgically treated for vitreoretinal complications of PSR, none developed postoperative ASI. The authors discussed the importance of collaboration between ophthalmic surgeons and the general medicine and hematology service in facilitating perioperative hydration, oxygenation and exchange transfusion, as necessary. Only five eyes required exchange transfusions, and no significant complications were reported in any of the eyes. Sympathomimetic agents as well as carbonic anhydrase inhibitors were also avoided in their series. The authors therefore argued that the risks associated with transfusions, which mostly included the risk of infectious hepatitis and HIV at the time, outweighed the potential benefits of preventing ASI. The authors were also reassured by their ability to manipulate other perioperative factors including adequate hydration, oxygenation and intraocular pressure control, in modifying the risk of ASI.²⁷

The only report of ASI published in the 1990s was in a case of a healthy male with sickle cell trait undergoing a SB procedure.²⁸ The authors advised the optimization of hypoxia perioperatively to prevent this complication. The present review found that the vast majority of ASI cases were reported to occur in patients undergoing SB procedures. However, in 2002, Leen et al. reported a case of ASI in a patient undergoing PPV, retinotomy and panretinal photocoagulation. Although this patient did not receive a SB, the authors postulated that the ASI likely developed due to prolonged intraoperative hypotension, elevated intraocular pressure during scleral depression and the use of panretinal photocoagulation.²⁹

Fortunately, over the last 16 years, 7 published studies of 108 eyes undergoing posterior segment surgery for vitreoretinal complications secondary to PSR did not report any ischemic complications related to SCD. This is likely associated with the adoption of advanced PPV techniques and the less popular use of SB procedures. Today, scleral buckles are often not placed high and broad, and the use of PPV has allowed for small incision

surgeries and shorter operating times. Enhanced wide-view visualization systems enable more feasible peripheral dissection and the introduction of valved cannulas have improved the surgeon's ability to manage intraocular pressure during surgery.³⁰

In 2009, Williamson et al. reported their series of 18 eyes undergoing 20-gauge PPV for PSR.³¹ In their study, all eyes with VH had improved postoperative vision, as did all eyes with RD. Although just under 40% of eyes endured iatrogenic breaks, there were no incidences of ASI in this cohort, despite none of the eyes having received perioperative exchange transfusions. Epinephrine was also avoided perioperatively. Additionally, 16 of 18 eyes underwent general anesthesia (GA) for the surgery, with the remaining two having received sub-tenon injection of local anesthesia.³¹ More recently, Chen et al. reported their vitreoretinal experience in PSR over a 12-year period.³⁰ As with previous reports, their results highlighted the guarded prognosis of patients with tractional RD secondary to PSR. Despite this, all eyes achieved anatomical success at final follow up and no cases of ASI were encountered. Although this group did not describe a standardized perioperative protocol, exchange transfusions were not performed in their series.³⁰

The largest consecutive cohort of vitreoretinal surgery outcomes in PSR was published by Ho et al. in 2018.³² During the period of 2009 to 2015, they reported on the outcomes of 20-gauge vs. 23-gauge PPV in 71 eyes and demonstrated that vision due to sight-threatening complications of PSR can be preserved or improved over a two-year follow up period. Their results indicated trends for 23-gauge PPV to be beneficial for visual and anatomic success, and for reducing intraoperative complications. Notably, none of the patients in this cohort received retrobulbar anesthesia or scleral buckles and exchange transfusions were not performed. Ischemic complications were not encountered in this study.³²

All of the 7 studies of 108 eyes published over the last 16 years were able to prevent ischemic complications, yet none described a consistent or standardized perioperative protocol. However, a number of common perioperative techniques may be playing key roles in the prevention of ocular and systemic ischemic complications from occurring: (1) most studies avoided retrobulbar anesthesia, (2) the use of exchange transfusions was not described in the studies, and (3) the use epinephrine was avoided. One case report also described the preoperative use of intravitreal anti-vascular endothelial growth factor to lessen the severity of neovascularization prior to surgery. This may be a promising avenue for future research in this population.³³ Our review did not identify controlled studies to test the benefit of employing any perioperative measures. Such studies would require the collaboration of multiple centres and surgeons to provide adequate statistical power to test these hypotheses, especially in the context of modern surgical techniques and very low and almost negligible ischemic complication rates. The optimization of perioperative techniques in this population may be more relevant in regions where modern vitrectomy techniques are not available.^{34,35}

The non-ophthalmic literature describing the perioperative management of patients with SCD was also briefly reviewed. The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study evaluated patients undergoing surgeries more invasive than ocular surgery including intraabdominal and orthopedic surgeries.³⁶ Patients receiving preoperative

transfusions were less likely to experience complications including acute chest syndrome. Another large multicentre study comparing aggressive and conservative transfusion regimens did not find significant differences in the rates of serious complications.³⁷ The utility of preoperative transfusions has been studied in patients with HbSS and HbS β thalassemia thus far, and studies recommend a hemoglobin level of 10 g/dL or greater.³⁸ Other perioperative considerations include intravenous hydration perioperatively and the encouragement of oral hydration as soon as feasible postoperatively.^{39,40} Additionally, preoxygenation using an inspired oxygen fraction of 100% in advance of intubation has also been recommended in patients with SCD. Intraoperative oxygen saturation should be maintained in the normal range and incentive spirometry has been described to help prevent acute chest syndrome.⁴¹ Recently, an evidence-based report of SCD management by expert panel members outlined the following perioperative recommendations: (1) in patients undergoing a surgical procedure involving GA, transfuse to a hemoglobin level > 10 g/dL, (2) consult a SCD expert in patients with more severe SCD.⁵

Hydroxyurea, a ribonucleotide reductase inhibitor, is a disease-modifying agent for patients with SCD and is administered to increase fetal hemoglobin levels. Hydroxyurea improves cellular deformability and increases nitric oxide release, and as a result, improves perfusion and reduces the likelihood of vasoocclusion.^{43,44} Evidence-based recommendations for the use of hydroxyurea in patients with SCD include: (1) A history of recurrent severe pain crises, (2) SCD-associated pain that interferes with quality of life, (3) severe or recurrent acute chest syndrome, (4) chronic symptomatic severe anemia, (5) pediatric patients (greater than 9 months in age) with SCD, (6) patients with comorbid chronic kidney disease.⁵ Although retrospective studies have suggested a potential protective effect of hydroxyurea in children⁴⁵ and in adults⁴⁶ with SCD from developing retinopathy, the long-term and perioperative role of hydroxyurea in patients with SCR has not been elucidated.

While surgical management of SCR is reserved for patients with RD and/or nonclearing VH, laser photocoagulation is commonly applicable for patients with PSCR. Scatter laser photocoagulation targets and damages the ischemic retina responsible for the production of vascular endothelial growth factor and should be applied anterior the area of neovascularization.⁴⁷ One should avoid heavy white-hot burns that may promote inflammation and tissue necrosis. The primary indication for laser therapy in patients with SCR is the development of Stage III disease (peripheral retinal neovascularization), prior to the development of VH and/or RD.⁴⁸ Specifically, patients with peripheral neovascularization greater than 60 degrees of circumference, bilateral involvement, large and elevated sea fans, rapid progression, and patients who are monocular may benefit from laser therapy.⁴⁷ Transpupillary laser therapy is considered to be the safest option, while transscleral diode laser is used alternatively in cases with significant media opacities.⁴⁹ A meta-analysis by the Cochrane Collaboration identified randomized controlled trials comparing laser therapy to no therapy in patients with PSCR and found that treatment may prevent loss of vision, and reduce the occurrence of VH especially in patients undergoing feeder vessel coagulation.⁴⁷ Overall, rates of retinal tear and detachment were not different between treatment and control arms. However, treatment with xenon arc laser was found to be associated with a greater risk of choroidal neovascularization.⁴⁷

Conclusions

This review identified and reviewed the vast majority of published studies of patients undergoing vitreoretinal surgery for PSR. Although ischemic complications are feared by ophthalmic surgeons, this review indicates that modern surgical techniques and careful preoperative planning have thankfully made such complications rare. Perioperatively, most studies avoided retrobulbar anesthesia and the use of epinephrine. Additionally, the use of exchange transfusions is seemingly not required to prevent ischemic complications in patients undergoing vitreoretinal surgery for PSR. Based on recommendations from the non-ophthalmic literature, collaboration between ophthalmic surgeons and general medicine and hematology specialists can help optimize perioperative planning, as some cases may require customized treatment.

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Table 1.

Characteristics of studies included in full-text review

Citation	Study Design	Patient Population	Sample Size	Surgical Procedure	Outcomes and Complications	Perioperative Management
Freilich and Seelenfreund. (1973)	Report of 3 cases	PSR with RD	3 eyes	SB (n=3)	All eyes had improved vision	Procedure was performed in hyperbaric chamber under 2 atm of oxygen
Jampol et al. (1982)²⁶	Retrospective Case Series	PSR with RD or VH	19 eyes	SB (n=4) Vitrectomy (n=5) Vitrectomy + SB (n=10)	ASI (n=1) Severe bleeding (n=2) Postoperative glaucoma (n=2)	Exchange transfusion to raise HbA to 40-60% Elimination of sympathomimetic use in anesthetic or topical preparations Supplemental O ₂ intra- and postoperatively Careful IOP monitoring
Pulido et al. (1988)²⁷	Retrospective Case Series	PSR with RD and/or VH	11 eyes	Multifunctional vitrectomy probe (n=5) 20G PPV (n=6) SB (n=6) Retinotomy (n=3)	No ASI	Internal medicine service assisted with perioperative hydration, supplemental O ₂ and exchange transfusion as needed Exchange Transfusion (n=5) Eliminated epinephrine in retrobulbar anesthesia Avoidance of CAI
Leen et al. (2002)²⁹	Case Report	PSR with RD	1 eye	PPV+Retinotomy+PRP	ASI	GA Exchange Transfusion
Mason (2002)⁵⁰	Case Report	PSR with MH	1 eye	PPV+MP	Visual Improvement	GA
Williamson (2009)³¹	Retrospective Case Series	PSR with RD, VH, ERM, and/or MH	18 eyes	20G PPV+MP Cryotherapy (n=5)	Re-bleeding (n=2) No ASI	GA (n=16), No Exchange Transfusion Subtenon's local anesthesia (n=2) Topical epinephrine avoided
Moshiri et al. (2013)³³	Case Report	PSR with RD and VH	1 eye	IVB, then PPV+MP +Endolaser	Visual improvement	Pre-treatment with IVB, GA
Georgalas et al. (2014)⁵¹	Case Report	PSR with chronic RRD	1 eye	SB and Cryotherapy	Successful re-attachment and visual improvement	Not Discussed
Chen et al. (2014)⁵⁰	Retrospective Case Series	PSR with VH, ERM and/or RD	15 eyes	PPV (n=15) SB (n=2)	Visual Improvement in patients with VH or ERM Guarded prognosis with RD No cases of ASI	No standardized protocol Exchange transfusions not performed
Wang et al. (2016)⁵²	Case Report	SCR+RD+VPT	1	PPV+SB+tumour removal +Endolaser	Visual Improvement	Not Discussed
Ho et al. (2018)⁵²	Retrospective Case Series	PSR with RD, VH, ERM and/or MH	71 eyes	20G PPV (n=39) 23G PPV (n=32)	23G may provide better functional outcome with fewer complications No ischemic complications	Subtenon's local anesthesia or GA Exchange transfusions not performed

PSR=Proliferative Sickle Cell Retinopathy; RRD=Rhegmatogenous Retinal Detachment; SB=Scleral Buckle; VH=Vitreous Hemorrhage; ASI=Anterior Segment Ischemia; IOP=intraocular pressure; PPV=pars plana vitrectomy; CAI=carbonic anhydrase inhibitor; GA=General Anesthesia; PRP=Panretinal photocoagulation; ERM=epiretinal membrane; MH=Macular Hole; MP=Membrane Peel; VPT=Vasoproliferative tumor