BRIEF CLINICAL REVIEW

Fluid Replacement Strategies in Sickle Cell Disease

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Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive condition that effects approximately 100,000 people in the U.S.[1] A missense mutation at chromosome 11 causes the substitution of valine for glutamine at position 6 in the beta-globin gene, resulting in the sickle hemoglobin phenotype.[1] This substitution renders the hemoglobin protein susceptible to abnormal polymerization in the setting of noxious environmental stresses such as hypoxia, acidemia, infection, or hypothermia. Once the hemoglobin polymerizes, the red blood cells (RBCs) adopt a pointed or "sickled" shape. This conformational change and resulting alterations in fluid dynamics of the microvasculature lead to the many physiologic consequences seen in SCD. However, recent studies have shown that individuals with SCD also experience chronic platelet activation, endothelial adhesion protein and cell adhesion protein activation, and chronically elevated acute phase reactants.[2–8] This raises the question of how relationships between acute and chronic vascular changes amongst people living with SCD drive sequelae of the disease.

The vascular changes described above increase the risk for thrombogenesis and microinfarction, which represent a common final pathway to the known complications of SCD. In addition to infection and anemia, acute complications of SCD include vaso-occlusive crises (VOC), acute chest syndrome, myocardial infarction, renal infarction, stroke, bone infarction, venous thromboembolism, priapism, and complications of pregnancy. Acute pain crises or VOCs are the most common reason for a sickle cell patient to seek care at an emergency department.[9] Experts hypothesize that VOCs are the result of microinfarctions of the bone and periosteum, which cause exquisite pain.[10] The appropriate treatment regimen for acute pain crises is not definitively known, but the mainstays of therapy for the last several decades include analgesia, fluid replacement, and identification and resolution of the underlying environmental cause.

The approach to treating VOCs appears to be more experience-based rather than evidence-based. In specific regards to fluid replacement strategies for patients with SCD who present in VOC, little data exists on what the optimal regimen may be. However, it is convention that patients with SCD should be volume resuscitated to euvolemia on admission and then maintained on hypotonic maintenance fluids throughout the admission if maintenance requirements cannot be met through oral intake. These recommendations are based on scientific generalizations from decades of small clinical studies, molecular modeling, and pathology studies, but no large randomized clinical control trials of this topic currently exist.

Chronic complications of SCD affect many organ systems and are a result of not only the above described vascular changes but also complications from therapy. Most notably, these include chronic kidney disease (CKD), retinopathy, avascular necrosis, leg ulcers, cardiomyopathy, pulmonary hypertension, seizure disorder, and hepatic dysfunction. A prospective cohort study of SCD patients spanning 7 years found substantially increased organ dysfunction despite a stable rate of VOC. Eighty percent of the cohort developed organ damage related to SCD, most commonly renal dysfunction, retinopathy, and avascular necrosis.[11] This study and a prior by the same investigators found no relationship between the rate of VOC admission and the development of end-organ disease from SCD.[12] A mainstay of therapy for sickle cell disease is hydroxyurea, which increases the concentration of fetal hemoglobin in circulation and reduces hospitalizations for VOCs.[13] Hydroxyurea therapy can cause a number of adverse side effects including, edema, superficial ulcerations on extremities, nail discoloration, mucocutaneous toxicity, pancytopenia, liver injury, and weakness.

Fluid Therapy in the Context of SCD

Fluid Therapy in sickle cell disease is poorly understood. It is unknown how much, what rate, or what type of fluid should be used to replete a sickle cell patient in a pain crisis episode. Therefore, these initial management decisions are typically made by consensus. Admittedly "consensus opinion" has evolved over time. In the 1970s, a patient with SCD presenting in crisis may have received 5% dextrose and 0.45% saline solution with or without additional amps of sodium bicarbonate at a rate of 5 mL/kg/hr or enough fluid for the patient to produce 3L of urine daily and noticeable decreases in his or her serum sodium and osmolality.[14] In contrast, a similar patient in the early 2000s may have received slightly less hypotonic fluid (2.5 mL/kg/hr).[15]

Actual clinical practices regarding fluid therapy in SCD vary across healthcare institutions. The Sickle Cell Disease Clinical Research Network PROACTIVE Feasibility Study, which enrolled 237 individuals with SCD at 25 clinical sites, showed the majority of individuals receive less than maintenance fluids when hospitalized with VOC. This was estimated by the

Halliday Segar Formula (100 mg/kg/day for the first 10 kg, 50 cc/kg/day, for the second 10 kg, then, 20 cc/kg/day for each additional kg). There were some differences observed between study sites.[16] Eight of 25 institutions provided more than half of their patients with 1 to 1.5x the maintenance fluid rate as calculated by the Halliday Segar Formula, whereas 7 of the 25 institutions provided less than 0.5x the maintenance rate to at least half of their patients. It is possible that those institutions providing less maintenance fluids were more likely to encourage oral fluid intake, but this information was poorly recorded. These findings support the notion that institutional practices and policies are not standardized where SCD patients in VOC seek care.

The rationale for fluid replacement in vaso-occlusive crises is based in molecular studies and physiologic phenomena. As mentioned previously, the morphology and stiffness of the red blood cell (RBC) changes following polymerization of sickle hemoglobin. The rate of sickle hemoglobin polymerization is inversely proportional to the mean cellular hemoglobin concentration (MCHC).[17,18] Earlier studies focused on strategies to maintain cellular integrity by reducing the efflux of intracellular K+, Cl-, and free water. In one study, investigators induced a hyponatremic state in three patients with SCD. By decreasing the plasma osmolality, they sought to increase the intracellular free water and therefore decrease the MCHC. These investigators found that two of the study subjects experienced 1 VOC during the 100-day period of induced hyponatremia and the other subject experience no VOCs.[19] Attempting to address MCHC, several laboratory based studies have focused on inhibition of the Ca2+ activated K+ channel and the K+/Cl- cotransporter on the RBC membrane with varying success.[18,20]

At the capillary level, the osmolality of intravenous fluid administered to a sickle cell patient in crisis may affect RBC dynamics in the microvasculature. Increased cell membrane stiffness can decrease transit times through capillary beds and therefore increase the risk of microvascular complications.[18] Individuals with SCD in VOC display increased cell membrane stiffness due to cell dehydration and hemoglobin polymerization.[21] One study demonstrated that exposing RBCs with normal hemoglobin to hypotonic fluid decreases cell membrane stiffness.[22] Another study, which examined RBCs with sickle hemoglobin specifically, showed that those RBCs exposed to isotonic fluids had increased stiffness, slower transit times, and increased propensity to microvascular occlusion compared to RBCs exposed to lower osmolality fluids in a microfluidic model of the human capillary system.[21] These studies lend some evidence to the consensus opinion that euvolemic patients should not be maintained on hyperosmolar or isotonic maintenance fluids.[10]

Sickle cell patients are thought to be perpetually hypovolemic secondary to hyposthenuria, a renal condition characterized by an inability to concentrate urine.[23] Therefore, these patients may develop pathologic diuresis of free water. The inability to concentration urine appears to be reversible with RBC transfusion to non-anemic levels in infants and children but becomes permanent in the adult population.[23,24] Hyposthenuria is not restricted to patients with sickle cell anemia. Those with sickle cell trait and sickle beta thalassemia are also affected.[25] The mechanism of hyposthenuria in sickle cell patients is unknown but may be related either to the presence of sickled-cells in the renal microvasculature (a place of low oxygen tension in the body) or to renal ischemia.[26]

Aggressive hydration of sickle cell patients to hypervolemic states may be harmful. The development of pulmonary edema is one of the earliest signs of hypervolemia, resulting in hypoxia, dyspnea, and atelectasis. Unfortunately, atelectasis is considered a risk factor for the development of acute chest syndrome (ACS), one of the most common pulmonary complications of sickle cell disease and responsible for up to 25% of sickle cell deaths in the hospital.[27] Experts also suggest that pulmonary edema can predispose a patient to ACS and prolonged hospitalization.[28] One study of 21 hospitalized patients with sickle cell disease who died unexpectedly found that 71% of the patients had some type of lung pathology, and of those patients, 47.6% had pulmonary edema.[29] Because aggressive hydration may not be benign to this special patient population, more investigation is needed to determine the most optimal fluid resuscitation during VOC crisis in order to hasten resolution of symptoms, avoid complications of fluid replacement therapy, and reduce unnecessary or even harmful utilization of resources.

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