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HEMATOLOGY | REVIEW ARTICLE

Sickle cell-induced ischemic priapism

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Abstract: Priapism is one of the complications of Sickle cell disease (SCD). Priapism can be classified into ischemic (low-flow), non-ischemic (high-flow), or recurrent (stuttering). Ischemic priapism affects up to half of all men with SCD. Therefore, education coupled with more research on treatment options may help the patients with SCD to avoid the social, psychological, and medical implications of this condition and its embarrassing complications. This paper will focus on the mechanisms underlying the development of ischemic priapism in SCD, current preventative treatment strategies, and future directions for improved management of this condition.

Subjects: Hematology; Immunology; Infectious Diseases

Keywords: ischemic priapism; sickle cell disease (SCD); hemoglobin S point mutation (HbS)

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1. Introduction

Sickle cell disease (SCD) is a common hemoglobinopathy with 8% of African Americans heterozygous for the hemoglobin S point mutation (HbS) (Motulsky, 1973). The glutamine at the sixth position of the β chain is replaced with valine, resulting in single point mutation in which thymine replaces adenine on the deoxyribonucleic acid structure. Hemoglobin S causes polymerization of hemoglobin and red cell sickling on exposure to low-oxygen tension and causes unsickling on oxygenation (Adediran et al., 2013).

The combined influence of these factors can result in a vicious cycle of hypoxia, inflammation, and acidosis resulting in increased sickling, vessel occlusion, and ischemia (Kumar, Fausto, Abbas, Cotran, & Robbins, 2004).

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PUBLIC INTEREST STATEMENT

Prompt identification and proper treatment of a priapism episode in males with sickle cell disease (SCD) is serious, as the end result of prolonged episodes of priapism can be ischemia and fibrosis in the corpus cavernosa of the penis, thereby leading to impaired sexual function and impotence. The type and severity of the complications of SCD vary depending on a variety of genetic factors including the presence of other types of hemoglobin, particularly persistent fetal hemoglobin (HbF). Priapism is a real emergency, and early intervention allows the best chance of functional recovery. Any therapeutic possibility that aids comfort and decreases the possibility of surgery and thus the likelihood of erectile dysfunction would be of great benefit to patients with ischemic priapism. There research for finding new preventative treatments including long-term low-dose PDE5 inhibitors to normalize NO downstream signaling and potential inhibition of adenosine signaling to minimize fibrosis following an episode of priapism.

Manifestations of SCD are extensive and usually secondary to ischemia from vessel occlusion and hemolysis from direct rupture of sickle cells that have lost normal red cell deformability that include cerebral vascular accidents, pulmonary hypertension, osteonecrosis, lower extremity ulcerations, and pain (Jesus & Dekermacher, 2009).

In the present study, we emphasize on one common complication, which is the development of prolonged, painful erections known as priapism that can significantly affect the quality of life in men with SCD. Priapism is an uncommon pathologic condition that causes a true disorder of penile erection that persists beyond or is unrelated to sexual arousal or absence of desire (Berger et al., 2001; Montague et al., 2003a). The condition may occur at all ages. Current data showed that the incidence rates of 1.5 per 100,000 people each year have been estimated among the general population (Eland, van der Lei, Stricker, & Sturkenboom, 2001). In patients with SCD, the prevalence of priapism is up to 3.6% in patients <18 years of age (Furtado et al., 2012), increasing up to 42% in patients ≥18 years of age (Adeyoju et al., 2002; Lionnet et al., 2012; Olujohungbe et al., 2011). Pathologically and clinically, priapism can be classified into two subtypes, namely the high flow (non-ischemic) variety and the low flow (ischemic) priapism. The latter is associated with SCD, and patients suffering from this particular disorder are more susceptible to greater complications. In addition, their long-term recovery is dependent on prompt and urgent intervention (Cherian et al., 2006). Reports of the prevalence of ischemic priapism range from 2 to 35% (Adeyoju et al., 2002; Bennett & Mulhall, 2008). On the other hand, high-flow priapism, which results from increased arterial flow caused by trauma, does not result in tissue ischemia and is not associated with increased risk (Winter & McDowell, 1988). There are significant differences between the mechanisms underlying high and low-flow priapism. Therefore, this article mainly focuses on low-flow priapism, which is significantly increased in patients with SCD.

2. Pathophysiology of priapism

The understanding of the pathophysiology of priapism has improved over the last few decades, mainly because of the lack of knowledge of normal erectile physiology. Penile erection involves a complex coordination of vasorelaxation and vasoconstriction signals from sympathetic and parasympathetic inputs in order to control the blood flow to the penis and allow for its engorgement (Andersson, 2001; Olujohungbe & Burnett, 2013). In its basal state, the vascular and smooth muscle is maintained by vasoconstrictive factors, thus allowing the penis to remain in a flaccid state for nearly 23 h each day (Andersson, 2001; Christ, Richards, & Winkler, 1997). When neurotransmitters are released to signal an erection, penile erection is eased by smooth muscle relaxation, permitting for increased arterial blood flow into the penis and trabecular cavernosal tissue swollenness (Andersson & Wagner, 1995). The swollenness reduces the venous outflow, thus permitting and sustaining penile enlargement (Fournier, Juenemann, Lue, & Tanagho, 1987). Studies on molecular mechanisms underlying penile erection have shown nitric oxide (NO) signaling to be a critical element in normal erections (Burnett, Lowenstein, Bredt, Chang, & Snyder, 1992; Rajfer, Aronson, Bush, Dorey, & Ignarro, 1992). NO is released by both nerve terminals and endothelial cells and is diffused into both arterial smooth muscle cells and trabecular cells to initiate vasodilation through the activation of the downstream cyclic guanosine monophosphate (cGMP) pathway (Andersson & Wagner, 1995; Bivalacqua, Musicki, Kutlu, & Burnett, 2012; Burnett, Bivalacqua, Champion, & Musicki, 2006b; Ignarro, 1990). Termination of erectile response occurs when phosphodiesterase type 5 (PDE5) hydrolyzes cyclic guanosine monophosphate (cGMP), thus inactivating the second messenger nucleotide and returning the penis to its flaccid state (Corbin & Francis, 1999).

3. Ischemic priapism classifications and etiology

3.1. Ischemic priapism

Ischemic priapism, also known as low-flow or veno-occlusive priapism, is a persistent erection marked by the rigidity of the corpora cavernosa and by little or no cavernous arterial inflow (Broderick et al., 2010). Studies have shown that ischemic priapism is found in 95and of cases (Broderick, 2012) and is the most common variant in patients with SCD. Thus, ischemic priapism is a medical

emergency with possibly profound consequences if left untreated. Initially, the patient complains of penile pain, and the examination reveals a rigid erection and flaccid glans. In episodes lasting ≥6 h (major priapism) (Ralph et al., 2009), histopathologic studies revealed time-dependent erectile tissue damage (Spycher & Hauri, 1986). This is followed by fibroblast proliferation and tissue necrosis within 24 h of the occurrence of such episodes (Kovac, Mak, Garcia, & Lue, 2013; Ralph et al., 2009) and can result in erectile dysfunction (ED), with predicted rates as high as 90and from episodes lasting ≥24 h (Broderick, 2012). Consequently, patients are recommended to seek medical care to avoid these episodes (Montague et al., 2003a). In addition, priapism can also result in major psychological and social sequelae (Addis, Spector, Shaw, Musumadi, & Dhanda, 2007).

Different etiologies have been described for priapism, including pharmacologic exposures, trauma, neurologic conditions, and idiopathic presentations. Hematologic disorders, e.g. glucose-6-phosphate dehydrogenase deficiency, SCD, and hereditary spherocytosis, have been observed in the case of ischemic priapism (Burnett & Bivalacqua, 2008; Emond, Holman, Hayes, & Serjeant, 1980; Prabhakaran, Jacobs, Smaldone, & Franks, 2007). While SCD itself is a crucial risk factor, the occurrence of other SCD complications, including leg ulcers, ischemic stroke, and vaso-occlusive episodes, are also associated with priapism (Kato et al., 2009).

Most cases of ischemic priapism are reported to be idiopathic (Broderick et al., 2010; Pohl, Pott, & Kleinhans, 1986). Furthermore, the condition of ischemic priapism is associated with SCD, neoplastic disorders, hematologic dyscrasias, and the use of certain medications. It frequently arises after intracavernous injections of papaverine, phentolamine, and/or prostaglandin E1 (Broderick et al., 2010; Coombs, Heck, Guhring, Narus, & Mulhall, 2012; Jünemann, Persson-Jünemann, & Alken, 1990; Porst, 1996). Nevertheless, most of these cases are treated with papaverine-based combinations; the frequency of priapism is <1 and in the case of prostaglandin E1 (Porst, 1996).

Ischemic priapism is the most common etiology in childhood in patients with SCD, accounting for 63% of the cases. It is the main etiology in 23% of adult cases of priapism, with a lifetime likelihood of developing ischemic priapism accounting for 29–42% in SCD men (Bivalacqua et al., 2012; Broderick et al., 2010; Nelson & Winter, 1977).

Priapism resulting from regional infiltration or metastatic has not been extensively studied. Past reported cases specify that this is infiltrative and not a hemodynamic process like ischemic or high-flow priapism (Lin, Kim, Stein, & Khera, 2011). Fundamentally, advice for pharmacologic treatment is not likely to be effective. All of the affected men should be imaged with magnetic resonance imaging (MRI) and offered supportive care for primary cancer (Salonia et al., 2014).

3.2. Recurrent ischemic priapism

Recurrent ischemic priapism (RIP), also known as stuttering or intermittent, involves repetitive, painful episodes of prolonged erections. Erections are self-limited with intervening periods of detumescence (Levey, Kutlu, & Bivalacqua, 2012; Montague et al., 2003a). Most RIP episodes are brief, frequently occurring during sleep and lasting for <3 h (Morrison & Burnett, 2011). Though RIP is considered an indicator of major ischemic priapism, nearly 30% of the cases reported progression to major priapism (Emond et al., 1980; Olujohungbe & Burnett, 2013). In addition, more than 70% of SCD patients with a history of severe priapism have a history of RIP (Adeyoju et al., 2002).

The etiology of RIP is similar to that of ischemic priapism. SCD is the most common cause of RIP. The cause can also be idiopathic and may infrequently be due to neurologic disorder (Broderick & Harkaway, 1994). The underlining mechanism is similar to that of other types of ischemic priapism: insufficiency of endothelial NO in the penis causes down-regulation of its specific downstream effectors, cGMP-dependent protein kinase including PDE5 dysregulation (Champion, Bivalacqua, Takimoto, Kass, & Burnett, 2005; Sauzeau, Rolli-Derkinderen, Marionneau, Loirand, & Pacaud, 2003).

4. Mechanisms underlying sickle cell-induced priapism

Although the low-flow state and anatomic factors contribute to making erectile tissue disposed to ischemia and sickle-induced pain, ischemic priapism may also result from decreased penile venous NO concentration, resulting in vasoconstriction, reduced blood flow, deoxygenation, and sickling (Nolan, Wyszynski, Farrer, & Steinberg, 2005).

NO is a powerful vasodilator and key to tumescence; however, free NO is readily scavenged in the body by hemoglobin. It is converted to iron-nitrosyl hemoglobin (HbFeNO) following reaction with deoxyhemoglobin and to nitrate plus methemoglobin following reaction with oxyhemoglobin (Reiter et al., 2002). The capability of hemoglobin to scavenge NO in the body is normally reduced by its compartmentalization within RBCs, which results in a cell-free and consequently, hemoglobin-free zone adjacent to the vessel endothelium due to laminar blood flow. Furthermore, the occurrence of the cell membrane, cytoskeleton, and other factors increase the diffusion distance between NO and hemoglobin. Consequently, hemoglobin contained in RBC has <0.2% of the scavenging capacity of free hemoglobin (Liao, 2002). Due to the chronic intravascular hemolysis in SCD patients, there is a change in the NO regulation. SCD patients have elevated free hemoglobin concentrations compared to normal subjects (Reiter et al., 2002).

Other reports have also associated risk for priapism with markers of hemolysis. An elevated count for lactate dehydrogenase (LDH), bilirubin, and reticulocyte was noted in SCD men who experienced priapism compared with SCD men who had never experienced an episode of priapism (Melman, Serels, & Series, 2000).

5. Diagnostic evaluation of priapism

The purpose of initial diagnosis lies in distinguishing between ischemic and non-ischemic priapism. A proper evaluation is critical because ischemic priapism is a urological emergency. Therefore, history, physical examination, imaging, and laboratory testing are useful tools to determine both the etiology and subsequent action modality in such cases.

5.1. History and physical examination

The degree of pain can help differentiate the painful ischemic priapism from non-ischemic priapism, which is usually painless. Specific points in the history including duration of erection, circumstances associated with onset, associated conditions (SCD or coagulation disorders), a history of previous episodes, pharmacotherapy, prior treatment, and previous erectile function will allow the establishment of the etiology (Nelson & Winter, 1977; Melman et al., 2000).

Physical examination of the genitalia, the perineum, and the abdomen by inspection and palpation is done to determine the degree of tumescence, in addition to the overall signs of hematologic malignancy, trauma, or evidence of hemolytic disease. Unlike non-ischemic priapism, ischemic priapism is characterized by the rigidity and tenderness of the cavernosal body with the absence of penis/glans involvement (Anele, Le, Resar, & Burnett, 2015; Broderick et al., 2010; Burnett & Bivalacqua, 2011).

5.2. Penile arterial blood gas

Cavernous blood gas analysis can be used for direct visualization and evaluation of penile blood, thus helping to distinguish between the different types of priapism (Lue, Hellstrom, McAninch, & Tanagho, 1986). In non-ischemic priapism, the blood is oxygenated and bright red in color with cavernous blood gas values of a partial pressure of oxygen (pO_2) >90 mm Hg, partial pressure of carbon dioxide (pCO_2) <40 mm Hg, and pH 7.40, consistent with normal arterial blood at room air. Conversely, in patients with ischemic priapism, the aspirated blood is hypoxic and dark, and typical pO_2 <40 mm Hg, pCO_2 >60 mm Hg, and pH < 7.25 (Montague et al., 2003a).

5.3. Imaging

Penile imaging using color duplex ultrasonography (CDU) is recommended for diagnosing ischemic priapism. This serves in conjunction with penile blood gas sampling to further differentiate ischemic priapism from non-ischemic priapism (Bertolotto et al., 2003; Hakim, Kulaksizoglu, Mulligan, Greenfield, & Goldstein, 1996; Lue et al., 1986). Ischemic priapism is demonstrated by decreased or absent cavernosal arterial flow, whereas non-ischemic priapism is characterized by normal to high arterial flow velocities in cavernosal arteries (Bertolotto, Zappetti, Pizzolato, & Liguori, 2008; Feldstein, 1993; Montague et al., 2003a).

Although penile MRI is not a routine workup, it has been shown to present an accurate imaging method to assess the viability of smooth muscles in patients with priapism. The advantages of MRI include detection of unusual conditions such as malignant infiltration and segmental cavernosal thrombosis and reliable prediction of non-viable smooth muscle within the corpora after episodes of priapism (Burnett & Bivalacqua, 2007).

5.4. Laboratory testing

Laboratory testing should include complete blood count test and coagulation profile test to evaluate the degree of anemia and detect signs of other hematological diseases. Urine toxicology and drug screens can be used to determine the use of pharmacotherapeutic or recreational drugs (Bennett & Mulhall, 2008; Montague et al., 2003a). Reticulocyte counts and hemoglobin electrophoresis may detect the presence of SCD/trait or other hemoglobinopathies (Montague et al., 2003a). Finally, other hematologic tests, such as serum lactic dehydrogenase level, a marker of intravascular hemolysis, and glucose-6-phosphate dehydrogenase testing, may also be useful and informative (Montague et al., 2003a; Ralph et al., 2010). Although these laboratory investigations are valuable for differentiating the possible causes of priapism and its treatment, it is essential to note that these tests should not preclude rapid treatment and influence management of acute episodes (Levey, Segal, & Bivalacqua, 2014).

6. Management of priapism

6.1. Management of ischemic priapism

Acute ischemic priapism is an emergency condition. Therefore, an immediate and rapid step-wise intervention is compulsory for its treatment. The goal of the treatment should be to re-establish penile flaccidity, without pain and avoid subsequent chronic damage to the corpora cavernosal. In several cases, penile edema may persist, with ecchymosis and a partial erection that could finally mimic unresolved priapism.

The abnormal regulation of the NO pathway and its downstream signaling may be the key factor in the development of priapism in patients with SCD. As stated earlier, NO is a powerful vasodilator, however, free NO is readily scavenged by hemoglobin (Hb) in the blood. NO is converted to nitrate plus methemoglobin following reaction with oxyhemoglobin and to iron-nitrosyl hemoglobin following reaction with deoxyhemoglobin. NO scavenging develops a reduced expression of downstream regulatory molecules including PDE5 that normally degrades cGMP, which is the second messenger in NO signaling (Reiter et al., 2002). The regulation of PDE5 by cGMP and its effector, cGMP-dependent protein kinase (PKG) is complex. The regulation of PDE5 by cGMP and its effector, cGMP-dependent protein kinase (PKG) is complex. Although cGMP is the substrate for PDE5, it can bind at an extra allosteric site to enable the modification of the PDE5 conformation thus revealing a phosphorylation site. The site can be phosphorylated by PKG, leading to the subsequent increases in the PDE5 activity. In penile tissue, the promoters, which regulate the expression PDE5 isoforms, are responsive to increase the cGMP concentrations. So, cGMP stimulates the PDE5 expression to control its own degradation, stating that agents that increase cGMP levels could enhance PDE expression (Burnett, Bivalacqua, Champion, & Musicki, 2006a; Lin, Chow, Lau, Tu, & Lue, 2002).

Table 1. Types of surgical shunt techniques for ischaemic priapism

Distal shunts	
Percutaneous distal shunts	
Winter shunt	Large biopsy needle is inserted through glans into corpora cavernosum several times creating many fistulae
Ebbehoj shunt	No. 11 blade scalpel is percutaneously passed several times through glans into corpus cavernosum creating openings in the tunica albugenia resulting in larger fistulae
T-shunt	Modified Ebbehoj using No. 10 blade scalpel and turning scalpel 90° when pulling out creating 'T-shaped' openings in tunica albugenia
Open distal shunt	
Al-Ghorab	A 1 cm incision is made distal to coronal sulcus with excision of 5 × 5 mm cone segment of distal tunica albuginea from each corporal body
Burnett snake Maneuver	Modification of Al-Ghorab shunt. A Hegar dilator is used to evacuate ischemic blood through a distal tunical window
Proximal shunts	
Open proximal shunt	
Sacher or quackels shunt	In lithotomy position, bulbocavernosus muscle is dissected from corpus spongiosum and 1 cm staggered ellipses of tissue are incised/excised from spongiosal/corporal bodies, and the defects anastomosed together
Corporosaphenous vein or superfacial/deep dorsal vein shunts	
Barry shunt	The superficial or deep dorsal vein is ligated and anastomosed to the corpora cavernosa
Garyhack shunt	The saphenous vein is ligated and anastomosed with corpora cavernosa

Source: Mulhall, Incrocci, Goldstein, and Rosen (2011, p. 269).

First-line treatments in episodes lasting >4 h are highly recommended before any surgical treatment. Furthermore, patients often report using strategies such as exercise, warm or cold compresses, oral hydration, and ejaculation with widely varying levels of success (Adeyoju et al., 2002; Olujohungbe & Burnett, 2013). As mentioned earlier, the most common complication of priapism is ED, which can occur in as many as 59% of cases (Berger et al., 2001; Montague et al., 2003a; Morrison & Burnett, 2011). Still, recovery of erectile function may be seen in up to 44% of patients who have experienced priapism for 24–36 h. Therefore, time-to-time problems can harm the erectile tissue, and timely treatment is essential to avoid such problems (Bennett & Mulhall, 2008). Overall, the medical therapy for ischemic priapism primarily focuses on decompressing the corporal bodies and restoring arterial blood flow, thus reducing ischemia and the risk of tissue necrosis or injury, in addition to reducing pain (Montague et al., 2003a).

First-line treatment for ischemic priapism is the aspiration of blood and irrigation of the corpora cavernosal, in combination with intracavernous α-agonist injection therapy (Berger et al., 2001). A better resolution of ischemic priapism was achieved after injection of a sympathomimetic agent with or without irrigation (43–81%) compared to aspiration with or without irrigation (24–36%) (Montague et al., 2003a). Phenylephrine is the desired sympathomimetic agent because of its lower risk profile for systemic cardiovascular adverse outcomes compared to other agents (Burnett & Bivalacqua, 2011). Nevertheless, if phenylephrine is unobtainable, other α-adernergic agonists such as ephedrine, epinephrine, norepinephrine, or metaraminol, may be used (Montague et al., 2003a). Additionally, the possibility of post-priapism ED is lower when sympathomimetic agents are used (Montague et al., 2003a).

For ischemic priapism especially related to SCD, medical treatment such as intravenous hydration, oxygenation, alkalinization, and exchange transfusion may be performed. However, these interventions should never head the first-line therapy for ischemic priapism (Berger et al., 2001; Broderick et al., 2010; Burnett & Bivalacqua, 2011; Montague et al., 2003a).

Extended durations, typically greater than 24 h, are unlikely to resolve with intracavernous injection/irrigation therapy alone. Consequently, these patients may be advised to consider more instant surgical shunting after a trial of intracavernous injection/irrigation (Berger et al., 2001; Montague et al., 2003a, 2003b). The purpose of surgery is to make a channel or fistula that permits the deoxygenated blood to drain from the corpora cavernosal (Montague et al., 2003a). There are four subdivisions of shunts: percutaneous distal shunts, open distal shunts, open proximal shunts, and vein anastomoses (Table 1) (Burnett & Sharlip, 2013). For all the aforementioned techniques, the patient should receive perioperative antibiotics covering skin flora (Levey et al., 2014). Presently, inadequate data preclude a recommendation of greater productivity for one shunt over another, grounded on accurate outcome estimations. For all surgical procedures, the urologist should have a detailed discussion with the patient describing the indications, risks, and benefits of the surgical procedure. As priapism can be a controversial issue, it is crucial to give clarification to the patient, notifying him that the prolonged duration of priapism alone is a risk factor for ED and that any shunt procedure itself might not change that risk involved. An open distal shunt may be performed if these attempts at distal shunting are unsuccessful. The Al-Ghorab shunt comprises excising a portion of the tunica albuginea from the tip of the corpora cavernosa bilaterally thus allowing efficient drainage of blood from the penis, in addition to minimizing the possibility of spontaneous shunt closure.

A modification of Al-Ghorab shunt known as the Burnett "snake" maneuver involves tunneling the corporal bodies through the distal tunical defect with a Hegar dilator, which helps in corporal drainage. This procedure has been effectively used in men who experienced refractory priapism and who had previously undergone ineffective surgical attempts at priapism decompression. Some of these improved distal shunt techniques, particularly the Burnett snake maneuver and the T shunt (with or without tunneling), have proved to be highly successful monotherapies for priapism of extended durations (more than 48 h) (Brant, Garcia, Bella, Chi, & Lue, 2009). With the failure of distal shunts, other options like open proximal shunts, namely the Sacher (bilateral staggered corporospongiosal) or Quackels (unilateral corporospongiosal) shunts have also emerged.

Vein anastomoses employed as shunts have also been described for the treatment of refractory priapism. These include the Barry and Grayhack shunts, where a window is created in the corpus cavernosum, with a shunt created by anastomosing the deep dorsal vein or saphenous vein respectively (Nixon, O'connor, & Milam, 2003).

Penile prosthesis implantation should be used for the treatment of acute ischemic priapism episode, particularly in the context of priapism duration exceeding 72 h, where complete ED is possible to arise (Ralph et al., 2009; Upadhyay, Shekarriz, & Dhabuwala, 1998). Furthermore, it may also be done to help the resumption of sexual intercourse in cases where priapism has caused a significant penile deformity or erection loss (Bertram, Carson, & Webster, 1985). Proposed advantages of immediate penile prosthesis implantation in the context of acute priapism include treatment of the inevitable ED, resolution of the priapic episodes, avoidance of possible complications and failures of shunting therapies, and prevention of penile shortening (Monga, Broderick, & Hellstrom, 1996; Ralph et al., 2009; Rees et al., 2002; Tausch, Evans, & Morey, 2007).

Some experts now advocate for the use of penile prosthesis earlier in patients representing with recurrent refractory episodes of priapism or those who have already undergone shunt procedures in the past. Infections can arise few months after surgery and a usual sign is persistent, unchanging, or even increasing pain. Several studies have shown that diabetic patients are more likely to develop an infection. However, the introduction of new surgical instruments and new infection-resistant material has radically reduced the risk of intra- and postoperative obstacles and the need for correction

surgery. Yet, surgical expertise and a thorough sterility rules remain as the major requisites to guarantee the success of a penile prosthesis implant (Bettocchi et al., 2008).

6.2. Treating recurrent priapism

The treatment of recurrent priapism is aimed at preventing any future episodes so as to reduce the significant risk of progression to a major episode (Anele & Burnett, 2015). This treatment goal can usually be achieved using pharmacology. The management of each acute episode should follow the guidelines for episodes of ischemic priapism, namely aspiration/irrigation in combination with intracavernous injections of α-adrenergic agonists including 5α-reductase inhibitors (5-ARIs), and gonadotropin-releasing hormone agonist (GnRH agonist, GnRH–A) (Bivalacqua et al., 2012; Levey et al., 2012; Morrison & Burnett, 2012).

Following the current guidelines for episodes of priapism, men consulting for stuttering priapism are referred to a hematologist to rule out the presence of blood dyscrasias. In addition, patients with recurrent priapism are taught self-injection of a prescribed α-adrenergic sympathomimetic as a management approach after 1–2 h of recurrent priapism. However, this intervention is not preventative (Montague et al., 2003a).

Hydroxyurea is the only US Food and Drug Administration-approved drug for treating SCD. It inhibited DNA synthesis during the S-phase of the cell cycle and increased fetal hemoglobin (HbF), thus decreasing hemoglobin S (HbS) polymerization and sickling (Anele, Morrison, & Burnett, 2015). While hydroxyurea can decrease vaso-occlusive crises and increase life expectancy in SCD patients, its efficiency in preventing recurrent priapism is unclear.

Hormonal manipulation aims at smothering the levels of testosterone circulating in the body to suppress the action of androgen on penile erection (Bivalacqua et al., 2012; Yuan, DeSouza, Westney, & Wang, 2008). Hormonal agents such as antiandrogens, 5-ARIs, and GnRH agonist with or without intermittent self-administration of sympathomimetic agents for acute episodes have been shown to be successful medical management options for some patients with recurrent priapism (Berger et al., 2001; Feldstein, 1993; Levey et al., 2012; Montague et al., 2003a). Potential side effects may include hot flushes, gynecmostia, impaired erectile function, loss of libido, and asthenia (Goetz & Burnett, 2014; Morrison & Burnett, 2012).

PDE5 inhibitors have shown potential in the prevention of RIP of varying etiologies. Oral PDE5 inhibitors including sildenafil and tadalafil are frequently used as medical treatment for ED. However, recent scientific evidence has proved the inconsistency of their effects in lessening RIP (Burnett, 2003; Burnett et al., 2006a; Bivalacqua et al., 2009; Champion et al., 2005). This suggests that priapism may be related to abnormal vascular homeostatic actions in the penis. The leading proposal regarding the abnormal signaling of the endothelium-derived NO and PDE5 signal transduction pathway in the penis suggested that RIP may be caused by reduced NO availability (Hannan et al., 2013; Kato, 2012; Shalev, Staerman, Allain, Lobel, & Saiag, 1999). A small case series done by Anele and Burnett (2015) showed that daily PDF5 therapy reduced ischemic priapism episodes in men with shuttering priapism. None of the patients informed any adverse events related to the therapy except only one SCD patient, who had SCD-associated priapism with a history of severe recurrent episodes and did not respond to the treatment. At present, there are long-term data available regarding therapy with PDE5 inhibitors in men suffering from recurrent idiopathic priapism. The results show that PDE5 inhibitors lessened priapism in men with idiopathic priapism, in addition to SCD-associated priapism, without affecting their normal erectile capacity (Pierorazio, Bivalacqua, & Burnett, 2011; Segal, Readal, Pierorazio, Burnett, & Bivalacqua, 2013). PDE5 inhibitors are a likely new preventative treatment for priapism. The use of PDE5 inhibitors is an emerging and successful therapy techniques for the preventative treatment of stuttering episodes. The PDE5 inhibitors can be either used during the initial phases or in combination with the concomitant administration of intracavernosal phenylephrine injections for the treatment of the acute episodes of priapism (Montague et al., 2003a). The ongoing research in this field is set to achieve some very significant outcomes in this avenue and

suggests that PDE5 inhibitors can be a useful preventative therapy for mild-to-moderate cases of stuttering priapism with minimal side effects. Larger trials are currently concerning the use of PDE5 inhibitors in the management of stuttering ischemic priapism are in the pipeline. However, its use is currently contraindicated by the packaging labels and therefore, considered investigational now (Bivalacqua & Burnett, 2006).

PDE5 inhibitor therapy is the first pharmacotherapy that targets the true molecular biology of priapism. Although quite premature in its efforts to translate bench science to the clinic, novel discoveries in basic science research delving into opiorphins and adenosine as signaling pathways that may play a role in the development of stuttering ischemic priapism, represent potential targets for future therapies directed at the prevention and thus treatment of priapism (Mantadakis, Cavender, Rogers, Ewalt, & Buchanan, 1999). Placebo-controlled, randomized clinical trials are presently in progress for establishing their competence.

7. Conclusion

Priapism is a real emergency, and early intervention allows the best chance of functional recovery. There are several possible etiologies of the patient's priapism. However, it appears that SCD was likely a predisposing factor, and we suppose that this represents an important public health issue. More awareness about priapism complication amongst SCD patients should be considered in order to reduce the incidence of impotence and infertility among them. Any therapeutic possibility that aids comfort and decreases the possibility of surgery and thus the likelihood of erectile dysfunction would be of great benefit to patients with ischemic priapism. There is hope for new preventative treatments including long-term low-dose PDE5 inhibitors to normalize NO signaling to minimize fibrosis following an episode of priapism.

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