What is the effectiveness of surgical and non-surgical therapies in the treatment of ischemic priapism in patients with sickle cell disease? A systematic review by the EAU Sexual and Reproductive Health Panel


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Abstract

Sickle cell disease (SCD) is an inherited hemoglobin disorder characterized by the occlusion of small blood vessels by sickle-shaped red blood cells. SCD and is associated with a number of complications, including ischemic priapism. While SCD accounts for at least one-third of all priapism cases, no definitive treatment strategy has been established to specifically treat patients with SC priapism. This aim of this systematic review was to assess the efficacy and safety of contemporary treatment modalities for acute and stuttering ischemic priapism associated with SCD. The primary outcome measures were defined as resolution of acute priapism (detumescence) and complete response of stuttering priapism, while the primary harm outcome was as sexual dysfunction. The protocol for the review has been registered (PROSPERO Nr: CRD42020182001), and a systematic search of Medline, Embase, and Cochrane controlled trials databases was performed. Three trials with 41 observational studies met the criteria for inclusion in this review. None of the trials assessed detumescence, as a primary outcome. All of the trials reported a complete response of stuttering priapism; however, the certainty of the evidence was low. It is clear that assessing the effectiveness of specific interventions for priapism in SCD, well-designed, adequately-powered, multicenter trials are strongly required.
Introduction

Priapism is defined as painful, persistent and prolonged erection lasting 4 hours or more.  
There are three types of priapism: low flow priapism (ischemic (IP) or veno-occlusive), high  
flow priapism (non-ischemic or arterial) and stuttering priapism. Nearly 95% of priapic  
episodes can be attributed to low flow priapism. There are several causes for IP, including  
pharmacological agents, infections, neoplasms, neurogenic disorders, and hematologic  
dyscrasias such as sickle-cell disease (SCD)  

SCD is an inherited hemoglobinopathy caused by inheritance from both parents of an altered  
beta-globin chain gene, of which one at least is beta S. SCD accounts for at least one-third of  
all priapism cases. Sub-Saharan Africa, the African diaspora, Arabic countries, the  
Mediterranean, and South America are the geographic areas with the highest prevalence of  
SCD. IP in SCD occurs in all age groups; however, the peak incidence is between 5 to 10 and  
20 to 50 years of age. In a study from Jamaica, SCD related IP had a peak incidence between  
the ages of 20 to 25 years, whereas the onset of priapism mainly occurred between 5 to 45  
years. Almost ninety percent of males with SCD experience at least one episode of priapism  
by the age of 20 years of age. The central pathophysiology of SCD is hemoglobin  
polymerization which results in erythrocyte rigidity and vaso-occlusion. Vaso-occlusion in the  
corpora cavernosa manifests itself as acute or recurrent IP or so-called stuttering priapism.  
A better understanding of the pathophysiology of SCD has led to the emergence of therapies  
novel in this field. Interventions for SCD-related IP aim to resolve acute episodes and prevent  
or reduce the frequency of recurrent attacks. These interventions can be classified as non-  
surgical options (such as hydration, analgesia, pharmaceutical agents, red blood cell  
transfusion, and blood alkalization) and surgical options (such as washouts, shunts, and penile  
implants). However, scant data are available in the literature reporting on resolution or  

prevention of IP episodes, thus making it challenging to provide a treatment algorithmic for SCD related priapism. In this systematic review, we aimed to assess the efficacy and safety of proposed treatment modalities (surgical and non-surgical) in the treatment of SCD derived IP and provide guidance in this challenging area.
Materials and methods

Search strategy, selection of studies and data extraction

The EAU Sexual and Reproductive Health Panel commissioned and undertaken the review. PICO was agreed after review by guideline office of EAU. The protocol for the review has been published and is available online (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=182001, PROSPERO Nr: CRD42020182001). A systematic search of Medline, Embase and Cochrane controlled trials databases (CENTRAL, CDSR) was performed up to August 2021. Abstract screening, full-text selection and data extraction were performed independently by two reviewers (MG and LB). Potential conflicts were resolved by discussion or with a third reviewer (KD). Only English language articles were considered and no date restriction was applied for the literature search.

Types of study designs included

All randomized controlled trials (RCTs), non-randomized comparative studies (NRCSs) and single-arm studies with ≥5 participants were eligible for inclusion. Case reports, commentaries, reviews, abstract-only studies and editorial commentaries were excluded.

Types of participants included

Eligible participants were children and adult male patients (with no age restriction) with a history of SCD who presented with an episode of ischemic priapism (acute or stuttering).

Types of interventions included

Non-surgical interventions comprised non-pharmacological or conservative interventions (hydration, exercise, masturbation, warm packs, cold bath), pharmacological methods aiming to address sickling (oxygen, alkalization, intravenous hydration, analgesics) or address/prevent priapism (α-adrenergic agonists such as pseudoephedrine and etilephrine, hormonal
manipulations of circulating testosterone by GnRH agonists or antagonist, antiandrogens or estrogens, digoxin, terbutaline, gabapentin, baclofen, hydroxyurea, PDE5is and exchange transfusion) were included. Surgical interventions included aspiration and irrigation of cavernosal bodies, shunt surgeries (distal and proximal) and penile implants.

Types of outcome measures included

Two primary outcomes were determined: 1) treatment success that was defined as the resolution of acute priapism within 15-30’ after the onset of treatment (defined as no need for further non-surgical/surgical interventions to resolve priapism episode) and the complete response of stuttering priapism (defined as no new episodes of stuttering priapism requiring further non-surgical/surgical interventions) at 3 and 6 months after treatment; and, 2) sexual dysfunction (erectile dysfunction), as reported subjectively or by objective measurements (such as International Index of Erectile Function) at 3-6 months.

Secondary outcomes included resolution of SCD-associated pain at 24 hours post-intervention (or as defined by trialists), association of SCD, priapism, exchange transfusion and neurological events (ASPEN) syndrome 3-6 months post-transfusion, and other adverse events (such as penile curvature/Peyronie’s disease, chronic pelvic pain) at 3-6 months post-intervention. A descriptive text was provided for studies where outcomes were not reported at the pre-specified time points.

Assessment of risk of bias

Risk of Bias for RCTs and NRCSs was assessed with the use of Cochrane/modified Cochrane RoB assessment tool, respectively⁹. For case series, a five-criterion quality appraisal checklist was used (Supplementary material).
Results

Quantity of evidence identified

Figure 1 outlines the flow diagram of the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). A total of 2626 abstracts were screened; 79 were extracted for further screening. Finally, a total of 44 studies met inclusion criteria with 3667 patients. These studies were composed of three RCTs\(^\text{10-12}\), and 41 observational studies\(^\text{13-53}\) (Table 1).

Characteristics of the included studies

Characteristics of RCTs

Only three RCTs were included in the final analysis. The first RCT analyzed a total of 11 participants who had at least two stuttering priapism attacks weekly (aged 18 to 29 years)\(^\text{10}\). The second RCT investigated a total of 78 patients (aged 14.5 to 46.1 years) who had a history of confirmed SCD-related stuttering priapism. This study did not specify the number of priapism attacks per week for inclusion, but they excluded patients who had an episode that lasted longer than 4 hours or required hospitalization\(^\text{11}\). The final RCT recruited 13 patients (aged 14 to 45 years) with SCD reporting IP episodes at least twice weekly\(^\text{12}\). In these all RCTs, pharmacological agents used to prevent IP attacks compared to placebo were stilboestrol 5mg\(^\text{10}\), sildenafil 50mg\(^\text{12}\), etilefrine 50mg, ephedrine 15mg, and ephedrine 30mg\(^\text{11}\).

Characteristics of observational studies

Most of the studies included in this analysis were observational studies (mostly case series)\(^\text{13-53}\).

RoB and confounding assessment of the included studies
The RoB summary and confounder assessment for the 3 RCTs 10-12, and 41 observational studies13-53 are presented in Fig. 1 and 2, respectively. Most RCTs had unclear risks concerning selection bias, performance and detection biases, while the risks of attrition and reporting biases were low. For all observational studies, the overall judgment of risk of bias was high.

Comparison of interventions

Primary outcomes – Resolution of acute priapism

Data from RCTs

This outcome was not applicable to the included RCTs 10-12.

Data from observational studies

Generally, patients with SCD-related priapism had complete acute spontaneous resolution or resolution with conservative measures (aspiration, irrigation, exchange blood transfusion, intracavernosal injection of sympathomimetics)23,28,30,33. In cases of failure of conventional methods, shunt procedures were utilized35,39,40. Patients with a longer duration of priapism (>48 hours) were more likely not to respond to medical management and undergo surgical procedures 44. In delayed cases who had previously been treated conservatively (priapism onset >1 day), exchange transfusion also seems ineffective in resolving acute priapism 34. (Table 2)

Primary outcomes – Complete response of stuttering priapism

Data from RCTs

In a double-blind crossover trial, stilboestrol 5 mg daily was shown to be superior over placebo in preventing priapic episodes 10. Eleven patients were randomly allocated to receive either placebo or stilboestrol 5 mg daily for 2 weeks after a 2-week baseline period. If a patient did not respond to a given treatment, he was shifted to the alternative treatment option. Nine patients completed the trial, of these 5 were randomized to receive placebo. Of the 5 placebo
patients, 4 patients’ priapic episodes were unchanged. Only one patient’s attack ceased immediately. However, a painful crisis emerged 6 days later in this patient, and he eventually was switched to stilboestrol treatment with 4 other patients. Stilboestrol treatment ceased attacks immediately in 4 of 5 patients and gradually in one. All the remaining patients allocated to stilboestrol arm responded to treatment, and no crossover was required (p =0.031, Fisher’s exact test) 10.

In another trial, no significant difference was found in the weekly total number of priapic episodes among the treatment groups (placebo, etilefrine 50 mg, ephedrine 15 mg and ephedrine 30 mg) compared to baseline pre-randomization period 11. However, this study was criticized due to attrition bias 6.

In a RCT study where 13 patients were allocated to receive either sildenafil 50 mg or placebo daily, no significant difference was found in controlling frequency of priapic episodes by 50% according to intention-to-treat or per-protocol analyses (p = 1.0). One out of 6 patients receiving sildenafil demonstrated a decrease in the frequency of priapic episodes, while 2 out of 7 placebo patients reported a reduction in frequency 12.

Data from observational studies

One study reported that etilefrine (25-200 mg) successfully treated priapic episodes in one of 3 patients 37. Virag et al. reported that receiving etilefrine either orally or by intracavernosal injection controlled priapic episodes in 5 of 6 patients with SCD 51. Another study reported a 72% success with 50-100 mg daily after a 10 to 48 months follow-up 41.

Muneer et al. reported that in etilefrine-resistance patients, the priapic episodes were controlled with cyproterone acetate. In cases of cyproterone acetate failure, penile prosthesis implantation has also been reported as a technique to prevent priapic episodes 37. (Table 2)

Hydroxyurea, an anti-neoplastic agent, was tested in preventing priapism episodes in 10 patients with SCD 36. While half of the patients had cessation of episodes, 40% of the remaining
patients had episodes lasting less than one hour. In another study, hydroxyurea successfully prevented priapic attacks after the maximal dose (20–35 mg/kg) was introduced (one to two months later) \(^4^5\). However, with the discontinuation of hydroxyurea therapy, priapic episodes reappeared.

In a study by Hoeh et al., ketoconazole, an antifungal agent, was administered to patients with recurrent ischemic priapism (200 mg for 6 months). Only one patient recurred (1/17) during the therapy. However, following the discontinuation of the treatment, only 5 patients remained recurrence-free \(^2^9\).

The effect of finasteride, a 5α-reductase inhibitor, in controlling the priapic episodes in patients with SCD was evaluated in a decreased-dose fashion (starting from 5 mg daily to 3 mg and 1 mg, 40 days each, a total of 120 days) \(^4^2\). Of the 35 patients, 46% had no recurrences, while the others experienced 1 to 15 recurrences during 11 months of follow-up. Higher doses (3 and 5 mg) were associated with fewer recurrences.

Insertion of penile implants was shown as a practical option in a case series of 5 SCD related recurrent priapism refractory to medical intervention and surgical shunting \(^4^3\). In another study, penile prosthesis implantation resulted in complete resolution of stuttering priapism caused by SCD \(^5^3\).

Exchange Blood transfusion has also been used in preventing SCD-related IP episodes. In general, blood exchange therapy was utilized after failure of other conservative measures such as aspiration, irrigation or injection of sympathomimetics \(^1^3,1^5,1^9,2^2-2^4,2^6,2^8,3^4,3^7,3^9,4^6,4^9,5^3\). In a study including 10 SCD-related IP patients, exchange transfusion fully controlled priapic episodes in 50% of the patients. In the same study, priapic episodes recurred in 20% of the patients after 4-8 months, while 30% failed to respond to the therapy \(^1^9\).

*Secondary outcomes - Erectile function*
Data from RCTs

This outcome was not assessed in the included RCTs 10-12.

Data from observational studies

Potency rates varied between 0-100% 16-18, 21-25, 28, 30, 46, 49-51. Only 3 studies objectively evaluated the sexual function parameters 14, 20, 22. Adetayo 14 used the Moloney, Elliot and Johnson grading system (Good, Fair and Poor) to evaluate the post-therapy erectile function, Chakrabarty et al. 22 assessed erection with radial rigidity (RigiScan). Bennett and Mulhall 20 evaluated the impact of priapism duration (<12 hours, 13-24 hours, 24-36 hours, >36 hours) with the IIEF in a consecutive series of 39 men. Spontaneous erections returned 100% of whom priapism duration was less than 12 hours. However, spontaneous erections only fully returned in 44% and 78% of patients whose priapic episodes lasted longer than 24-36 hours and 12-24 hours, respectively. No patients with priapism >36 hours duration had return of spontaneous functional erections.

Secondary outcomes – Resolution of SCD-associated pain

Data from RCTs

Resolution of pain was only reported in one trial. The pain level was evaluated using either a validated 0-10 linear analog pain chart or a traffic light color-coded pain scale. No significant difference among the 4 groups (placebo, etilefrine 50 mg, ephedrine 15 mg, and ephedrine 30 mg) was found regarding the average pain score per attack 11.

Data from observational studies

Most observational studies did not include the resolution of SCD-associated pain as a study endpoint. In a study with SCD patients who underwent penile aspiration and epinephrine irrigation for prolonged priapism, detumescence led to immediate pain relief 33. In another study, automated red blood exchange therapy failed to reduce pain in patients with SCD-related
priapism who did not respond to medical management options such as penile aspiration and irrigation. Similarly, increased penile pain was reported after transfusion therapy in children with SCD-related priapism. However, hydration and hypertransfusion therapy achieved prompt pain reduction (within 36 hours) in most of the children with SCD-related priapism.

Secondary outcomes – Adverse events

Data from RCTs

In the study where the effect of stilboestrol was compared with placebo in preventing the priapic episodes, no immediate or other untoward systematic side effects were assessed in the included RCTs.

In another RCT that evaluated the role of etilefrine (50 mg) and ephedrine (15 or 30 mg) in preventing stuttering episodes of priapism, tachycardia was the most frequently reported side effect (6/54 in etilefrine group and 2/17 in ephedrine 30 mg group), but it was self-limited and non-progressive. Other less frequently reported side effects for all treatment arms were palpitations (10/66), lack of sleep (12/106), handshaking (5/44), anxiety (5/43) and dry mouth (7/54). Significant differences were found among the 4 treatment groups in tachycardia (p=0.023) and palpitations (p=0.048), and the patients receiving etilefrine had a greater number of such episodes.

In the study of Burnett et al. that used sildenafil or placebo, reported immediate side effects included headache, flushing, abnormal vision, dyspepsia, nasal congestion, myalgia and hypotension. However, no significant differences were found between groups.

No other untoward systematic side effects were reported in the included RCTs.

Data from observational studies

Finasteride use to control priapic episodes was mostly associated with painless gynecomastia (6 out of 35 patients). Etilefrine was not associated with hypertension or erectile dysfunction.
either with oral or intracavernosal injections \(^{27,37,41,51,53}\). However, close monitoring was recommended in one study since the side-effects became apparent with longer term use \(^{41}\). In a retrospective study including 17 patients who used ketoconazole, no sexual dysfunction was reported whilst one patient suffered from nausea/vomiting \(^{29}\).

Several studies demonstrated that blood exchange transfusion is safe \(^{19,26,34,37}\). ASPEN syndrome was not reported in most studies \(^{19,22,26}\) but one study reported post-blood exchange mental confusion in 7 patients, which resolved several days after without any long-term sequelae \(^{34}\). In another study, only one patient (1/6) suffered from a non-regressive vascular cerebral accident 10 days after the exchange transfusion \(^{23}\).

Intracavernosal interventions and surgical procedures were associated with few adverse events. Intra-penile hematoma (0.05\%) rarely occurred after penile aspiration and epinephrine injection \(^{33}\). One case of subarachnoid hemorrhage was reported after injection of intracavernosal phenylephrine 500 mg/mL \(^{54}\). Urethrocutaneous fistula (1/5) \(^{15}\) and urethral injury secondary to shunt surgeries was also reported (1/34) \(^{31}\). Other rare complications following shunt surgeries include necrosis, gangrene and slough, chronic engorgement, diverticulum-like formation, and penile fibrosis \(^{25,39,40,48,52}\).
Discussion

Priapism is one of the most common urological acute emergencies. Approximately 10,000 men present with priapism annually and almost 30% require hospital admission. In the United States, about 1 in 5 patients presenting acutely with priapism has SCD. The phenotypic manifestations of SCD-related priapism include ischemic and stuttering types. SCD-related IP patients may encounter long-term physical and psychological consequences. Therefore, management goals of treating SCD-related priapism include immediate detumescence, preventing future priapic episodes, and preserving potency. With a better understanding of the pathophysiology of SCD, new targeted treatments can help clinicians. In this review, we sought to determine the safety and efficacy of treatment modalities to prevent and treat this condition.

From the perspective of the highest level of evidence, we found only 3 trials with small numbers of patients. In these trials, a total number of 4 different drugs (stilboestrol, sildenafil, etilefrine, and ephedrine) was evaluated with varying designs of trial.

One of the current systematic review’s primary outcomes, resolution of acute priapism, was not assessed in the included RCTs. None of the trials reported on detumescence. However, from the observational studies included in this SR, conservative therapies usually used as first-line strategies to resolve acute priapism have a success rate of between 0 to 100%. If conservative treatments fail, surgical measures ranging from distal shunts to penile prosthesis implantation can follow with a success rate between 0 to 100% (Table 2).

All included RCTs reported on the complete response of shuttering priapism in SCD patients. The use of oestrogenic hormones in the treatment of SCD related priapism was first advocated in 1960. Using the same approach, other case trials also supported the concept of
estrogenic effect either by suppressing pituitary function (stilboestrol) or targeting the pituitary gland (GnRH agonists) in SCD-related priapism cases. Although the exact mechanism of action is not fully clear, the anti-androgenic effect on the male hormonal axis or a direct effect on the cellular level of the sickled erythrocytes represents the most acceptable hypotheses. In one of the included RCTs, stilboestrol treatment was shown superior over placebo in preventing priapic episodes.

Relaxation and contraction of cavernosal smooth muscles are under alpha-adrenergic control. Therefore, the role of alpha-adrenergic drugs was also evaluated in several studies. In one RCT, no significant difference was seen between etilefrine or ephedrine and placebo, although several case series have demonstrated a protective effect of oral or intracavernosal etilefrine. Etilefrine is available as an oral or injectable form in many countries and is used by many clinicians as a preventative strategy in SCD-related priapism cases.

The logic of using PDE5i to prevent episodes of stuttering priapism is based on dysregulated PDE5 expression and activity in SCD. The paradoxical effect of sildenafil in controlling stuttering priapism was first shown in 3 patients with SCD and then in uncontrolled pilot studies. However, the first conducted RCT that explored the role of sildenafil in preventing recurrent IP in SCD patients failed to show a positive effect.

Rachid-Fildo et al. evaluated the role of finasteride, a 5-alpha-reductase inhibitor, in controlling SCD-related priapism. Although this was not a controlled-trial, the mean number of priapic episodes reduced from 22.7 to 2.1 after 4 months of daily finasteride use. Hydroxyurea, ketoconazole and cyproterone acetate were also used as preventative options with different success rates in the observational trials.

Penile prosthesis implantation is a treatment modality that is used in patients who do not respond to medical treatments and/or shunt surgeries. Ralph et al. assessed the immediate insertion of penile prosthesis for acute IP caused by some reasons including SCD.
as well; however, specific results for SCD related cases were not provided. Overall, penile prosthesis implantation was associated with a greater risk of infection, especially in those cases with previous shunt surgeries. Likewise, surgeons should also be aware of corporal tip weakness if a Winter shunt was previously performed. Only one study directly evaluated the role of penile prosthesis implantation in IP caused by SCD. Johnson et al. noted that men who underwent penile prosthesis implantation after an acute refractory episode of IP showed a complete resolution of their priapism symptoms. However, the data about optimum time for prosthetic surgery was not provided. In the same study, in one patient implantation of a penile prosthesis successfully controlled his priapic symptoms.

Blood exchange transfusion is another treatment option in SCD related IP cases to remove sickled-erythrocytes, especially when conservative measures fail. In some case reports, it was associated with serious neurological adverse events, ranging from severe headaches to increased intracranial pressure (including ASPEN syndrome), which required tracheal intubation and hyperventilation therapy. However, in the subsequent reports, the efficacy and the safety of blood exchange transfusion in resolving acute attacks with a success rate of 70-100% without any neurological side effects. The use of hydroxyurea treatment after transfusion therapy successfully prevented further episodes. In another study, regression of symptoms was complete in 56.7% of recurrent priapism cases with partial exchange therapy with only minimal side effects. McCarthy et al. applied exchange blood transfusion to 7 patients who failed to respond to conservative therapies. They showed a shallow success rate for the resolution of priapism. A recent study demonstrated that exchange blood transfusion provided partial resolution in addressing future episodes in the vast majority of the patients (87.5%), while no complete resolution was demonstrated in those cases (0%). The level of evidence is not robust enough to make any recommendation on the efficacy and safety of exchange transfusion in treating patients with SCD related IP.
Regarding our secondary outcomes, erectile function was not assessed in the included RCTs 10-12. Most NRCSs assessed erectile function after interventions subjectively (yes or no erection; normal or weak; poor or absent). Data obtained from observational studies indicate that only a few studies used validated questionnaires 14,20 or measured rigidity and tumescence activity to assess potency rates after the interventions 22. Other studies used subjective scoring systems and potency rates varied between 0-100%. Generally, potency rates were associated with the duration of symptoms before presentation, and interventions within the first 24 hours (especially if done in the first 12 hours) and seemed to better preserve potency. The potency rates after treatment were strongly associated with the duration of IP symptoms (longer the duration, worse the outcomes) 14,17,18,25, especially interventions within the first 24 hours (ideally 12 hours) and seemed to preserve potency with or without PDE5is 20. The impact of the specific type of intervention (either conservative or surgical) on the post-therapy potency rates are conflicting as some studies were in favor of conservative 15 whilst the others were in favor of surgical treatment 14,22,24. However, the age of the patient at intervention seems to affect potency rates inversely 22. To preserve future potency, surgical procedures should not be deferred, if the conservative therapy fail to resolve the priapism attack 14,20,22.

Another secondary outcome, resolution of SCD-associated pain, was investigated in only one RCT11. However, no significant difference was observed among study groups (placebo, etilefrine 50 mg, ephedrine 15 mg and ephedrine 30 mg). There are no studies directly comparing different treatment strategies concerning immediate side effects, and therefore, no recommendations can be provided. There is one ongoing study investigating the effect of ethyl phenylephrine and sildenafil on the prevention of erectile dysfunction in patients with SCD (ChiCTR1800017370) 75.

Focusing on treatment modalities, a large cohort of 12,547 participants with primary diagnosis of priapism, compared data between SCD and non-SCD patients. SCD-related priapism cases
required more blood transfusions (37.6% vs. 2.8%; P<0.001) and longer hospital stay (2.69 vs. 3.38 days [median]; P <0.001) However, the necessity of shunt surgery to resolve acute priapism in patients with SCD-related priapism was found statistically lower compared to non-SCD priapism cases. The overall rate of shunt surgery in the sample was 68.3%, but SCD patients were significantly less likely to receive operations (42.4% vs. 75.4%; P <0.001). In addition, SCD patients had their operations performed later during their admission. Therefore, according to the evidence provided, management of SCD related IP is no different from that of IP from non SCD and should be treated as a surgical emergency.

Limitations

Due to very limited number of high-quality studies, the level of evidence provided by this review is low. Also, heterogeneity in definitions, study designs, treatment modalities, participants and outcome measurements make this review inexact.
Conclusions

Conservative therapies seem to be reliable and safe treatment modalities that should be employed as an initial therapy for patients with SCD-associated priapism. In case of failure, surgical treatments should be employed for priapism resolution. Stilboestrol and sildenafil treatment may represent valid strategies to prevent future priapic episodes. The absence of good quality evidence with regards to management of SCD-related priapism requires well-designed prospective and RCTs with clear definitions and predefined outcomes of interest.
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Author Contributions

MG, LB, KD, SM and AS: Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results.

MG, SM and AS: Drafted or revised the manuscript:

SM and AS. Approved the final version.

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Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Legend to Figures and Tables

Figure 1: ROB assessment of RCTs

Figure 2: ROB assessment of observational studies
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