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REVIEW ARTICLE

Systematic review: interventions in sickle cell disease-related priapism in reducing overall morbidity, recurrence, and side effects

Revisión sistemática: intervenciones en priapismo relacionado con enfermedad de células falciformes (ECF), en reducción de morbilidad, recurrencia y efectos secundarios

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Abstract

Pediatric priapism is a rare, underreported urological emergency. Sickle cell disease (SCD)-related priapism cases should be assessed considering specific pathophysiologic characteristics. Chronic control of the disease has an impact on a patient's quality of life. A systematic review in different databases was done, for defining if management in All-type priapism in SCD patients was equally effective in reducing overall morbidity, disability and comorbidities, recurrence, and therapy-related side effects. Qualitative analysis was performed. Nine studies were included in the study; the majority were case series, and 300 patients were included in the analysis. The interventions and outcomes were clinically heterogeneous but displayed perspectives for further studies. This is the first analysis approach for a consensus for SCD-related priapism treatment. Studies with internal validity and causality designs are needed, to evaluate further causality relationships and establish evidence-based approaches. Etilefrine, Pseudoephedrine/etilefrine-5 inhibitors, and finasteride are promising strategies. Quality of life scores should be applied to these patients, and molecular studies should be developed for pharmacological designs.

Keywords: *Priapism. Sickle cell disease. Sickle cell anemia. Recurrence. Quality of life.*

Resumen

El priapismo pediátrico es una entidad poco común, sin embargo, es una urgencia urológica infranotificada. Los casos de priapismo relacionados con enfermedad de células falciformes (ECF) deben evaluarse teniendo en cuenta características fisiopatológicas específicas. El control crónico de la enfermedad tiene impacto en la calidad de vida del paciente. Se realizó una revisión sistemática en diferentes bases de datos, para definir si las intervenciones en pacientes con priapismo de todo tipo relacionado con ECF fueron igualmente efectivas en la reducción de morbilidad general, discapacidad, comorbilidades, recurrencia y efectos secundarios relacionados con la terapia. Se realizó un análisis cualitativo de nueve estudios; la mayoría series de casos, para un total de 300 pacientes. Las intervenciones y los resultados fueron clínicamente heterogéneos, pero mostraron perspectivas para futuros estudios. Este es el primer análisis de información para llegar a un consenso para el tratamiento del priapismo relacionado con la ECF. La perspectiva principal es la necesidad de estudios con validez interna y diseños elaborados para profundizar las relaciones de causalidad y el abordaje basado en la evidencia de esta condición. La etilefrina, los inhibidores de la PDE-5 y la finasterida son estrategias prometedoras. Se deben aplicar puntajes de calidad de vida a estos pacientes y se deben desarrollar estudios moleculares para diseños farmacológicos.

Palabras clave: *Priapismo. Enfermedad de células falciformes. Anemia de células falciformes. Recurrencia. Calidad de vida.*

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Introduction

Pediatric priapism is rare; however, it is a urological emergency. Defined as a prolonged full or partial penile erection lasting ≥ 4 h unrelated to the sexual stimulus[1]. The urological intervention aims to prevent outcomes such as penile disfigurement, shortening, erectile dysfunction (ED), psychological sequelae, and local endothelial and ischemic disease.

A common cause of priapism in children is sickle cell disease (SCD), accounting for 65% of overall cases[2,3]. SCD is a prevalent type of hematologic disease in our context, worldwide it has an incidence of 0.3-1.5/100,000 annually[4]. Most cases are reported in the fifth decade, overall prevalence in children is unknown and considered under-reported. SCD affects approximately 100,000 Americans, and one out of every 365 Black or African-American Births[5]. In Colombia, the frequency of this type of anemia is unknown; however, Pereira and Saenz reported that in the Pacific region of the prior country, 10% of the people have SCD traits, and 1% of major SCD; Heterozygous gene is a protector factor against *Plasmodium falciparum*. African-American people have a much severe presentation[6].

Complications of SCD include priapism, it has different physiopathological features, likewise, management should be systematically addressed in prevalent populations[7]. There are no current management consensus guidelines of priapism in children with SCD-related priapism, though multiple descriptions of case series[8], and reviews of scientific literature[9-12]. Studies addressing priapism in SCD[3] have shown that almost 35% of male patients with SCD have a priapism episode in their lifetime, the mean age of the first episode is 15 years, 25% are prepuberal and the majority are associated with a triggering factor, such as nocturnal erections, sexual activity, dehydration, fever, and cold exposure[13].

SCD mortality is mainly associated with infection complications and has decreased with the introduction of pneumococcal vaccine. Sickle cell-related deaths among Black or African-American children younger than 4 years old fell by 42% from 1999 through 2002[5]. However, the reduction in mortality requires a strict follow-up, comorbidity control, and insurance of quality of life.

Considering the above premises, even though SCD-related priapism is not the first cause of mortality, it has a direct impact on quality of life and, hence should be recognized and addressed properly in order to avoid ischemia, necrosis, fibrosis and ED.

Classification of priapism

Primary priapism is classified as ischemic (veno-occlusive and low flow), the most common, in which congestion and stasis cause ischemia; sluttering (Intermittent flow) is a poorly understood type, associated with a tonic cavernosal smooth muscle related to nitric oxide (NO) deficiency, SCD is the main cause[9]; and non-ischemic (Arterial, High Flow), mainly associated with pelvic, perineal and penile trauma, causing a laceration related arteriolar-sinusoidal fistula. It can also be classified into a primary or secondary, pharmacologically induced priapism is the secondary pediatric priapism[9,14-18].

Pathophysiology in SCD-related priapism

It includes detailed factors related to tumescence molecular basis: an increased capacitance of cavernosal arteries, further contraction of ischiocavernosus muscles, production of vasodilators factors such as NO, in addition to local stasis factors produced by cellular red blood cell changes secondary to drepanocytes. Ischemic priapism, prolonged erections are initiated by a variety of factors, leading to prolonged venous-occlusion and aberrant NO overproduction, causing glucopenia and lactic acidosis, muscle necrosis, and cavernosal fibrosis[19]. In SCD, there are several additional factors, such as sickling (adhesive interaction between erythrocytes) and microvascular obstruction, general endothelial dysfunction associated with a decreased bioavailability of NO, pseudoephedrine/etilefrine-5 (PDE-5), and RhoA[20], this could lead to compensatory overproduction of NO, or not. Low bioavailability of NO is associated with sluttering priapism or a mixed pathophysiology priapism. SCD-related priapism is much more complex than other etiology priapism and should be aimed considering this molecular basis for reducing overall morbimortality, disability, and recurrence.

Management

All types of priapism related to SCD should be assessed by experienced specialists. The initial, acute management includes detumescence maneuvers, analgesia, hydration, and the “First aid” guidelines include exercise, urination, and cold bath with or without ejaculation[21].

In the assessment, an active classification of the event should be done. Clinical history and physical examination should guide decisions. Initial examinations include urinalysis and culture, urine plasma toxicology, blood

counts, reticulocytes, sickle cell screen if unknown, lactate dehydrogenase, and liver function tests, arterial gasses are essential.

Ischemic priapism is mostly related with poor outcomes and prognosis; it is associated with more than 4 h of tumescence. First approaches include analgesia which is also aiming for tumescence inhibition[22], First aid, and corporal aspiration as first-line surgical intervention. Cold packs are associated with cytoprotective effects but could be a trigger in SCD-related priapism. Blood gasses could show lactic acidosis, hypercarbic, and glucopenic patients.

High Flow, non-ischaemic priapism, (also a patient with ischemic features and non-ischaemic blood gasses) should be managed with conservative interventions, teaching patients and parents the intermittent compression approaches. Follow-up should include a two weekly clinical decision unit and clinical review for 6 months. Some surgical interventions may be pertinent in cases of traumatic priapism. Interventions described in guidelines include super-selective embolization with dissolved material (autologous clot or gelatin foam) and transcorporal fistula ligation.

Surgical interventions for ischemic priapism

Corporal aspiration

It includes 0.9% saline lavages (1 mL/kg). A butterfly needle is inserted laterally at 3 or 9 o'clock position, careful insertion is needed for avoiding neurovascular bundle damage, and corpus spongiosum/urethral damage.

Intracorporeal injections (ICI)

Although it is described as the first line of intervention, the procedure includes waiting for corporal aspiration and lavage tumescence resolution, if detumescence is not achieved, sympathomimetic ICI should be performed, with strict cardiovascular monitoring. Injections are stopped when detumescence is achieved. The guideline recommendations[9] include an ICI of phenylephrine, a selective alpha 1 adrenergic agonist, 100-500 mg should be injected in adults, and less or more diluted for children, pediatric doses lack guidelines and evidence, only case series are reported. Some guidelines suggest using 100-mg aliquots of phenylephrine (0.5 mL of 200 mg/mL solution) at 5-10-min intervals in children aged 11 years (up to 10 times)[9]. Etilefrine is also used. Alpha 1 non-selective, sympathomimetics should be avoided, cardiovascular effects may be seen.

Bilateral distal T-shunts

If cavernosal aspiration and ICI are unsuccessful or recurrence is seen, this approach is described in guidelines. Shunts can be distal (cavernoglanular: percutaneous e Winter/T-shunt, or open e Al-Ghorab), proximal (cavernospongiosal e Quackels), or cavernovenous (saphenous e Greyhack). Distal is described to have lower complication rates[1]. In Broderick et al. series, it has been reported subsequent favorable erectile function in 75% of patients[1,20].

Other interventions

Described in guidelines, after recurrence or unsuccessful approach of previous lines, include Midcorporal corpotomies with or without "snake maneuver," and Quackels shunts. These approaches have not been described in children.

Exchange transfusions

Recent evidence that proposed series of exchange transfusions has shown limited evidence for this intervention[23,24].

Recurrent priapism

Sluttering priapism, the second more frequent type of SCD-Related priapism, is not managed differently from ischemic priapism; however, further interventions have been addressed to decrease the recurrence risk and ischemic presentation. Patients with > 2 h should go to the emergency department. The other pharmacological intervention group includes the alpha-adrenergic sympathomimetics PDE-5 inhibitors, hydroxyurea, Oral B-agonists, gonadotropin-releasing hormones agonists; all of which include acute and long control of symptoms.

PDE-5 inhibitors, short, and long acting have been reported successful, as exposed before the NO regulation in SCD is disrupted[25], associated with enzyme downregulation and sluttering priapism. Chronic use of PDE-5 inhibitors could upregulate the enzyme, ensuring better oxygen supply, and preventing ischemic penile crisis, and recurrence. Studies with chronic use of IPDE-5 inhibitors as long-term management have given results[26,27], no published consensus.

Alpha-adrenergic sympathomimetic drugs enhance detumescence process in acute phase, mainly by contraction of smooth muscle. Several studies have addressed alpha-adrenergic drugs, phenylephrine and etilephrine are the most studied ones[28,29]. Side effects of alpha-adrenergic drugs include cardiovascular response, palpitations, and blood pressure changes, which should be closely monitored. Furthermore, there have been described Phenylephrine ICI at home devices, and it has shown better results in follow-up studies in adults than in children due to the risk of trauma[30,31].

Hydroxyurea has been studied in all types of SCD crisis with favorable effects[32-34]. The safety of the therapy has several issues including myelosuppression[35].

Other therapies include Terbutaline, Gonadotropin-releasing hormone agonists, antiandrogens, estrogens, ketoconazole (testosterone synthesis inhibitor), and 5-a-reductase inhibitors, results are not conclusive.

Other comorbidities associated with SCD-related priapism

Considering the pathophysiology, there is an increased risk of cerebrovascular disease, accounting for nearly 21-25%. ASPEN Syndrome, an eponym for the association of SCD priapism, exchange transfusion, and neurological events, neurological symptoms should be addressed early for tissue salvage, the molecular basis is associated with vasoactive dysregulation in penile tumescence crisis[23].

Materials and methods

Selection and description

Systematic Review of all Clinical Trials, Randomized Clinical Trials, Clinical case series with three or more patients for outcomes related to All-type priapism in SCD patients, in adult and pediatric age, who received any intervention, independent of the type of priapism, physical examination presentation, and previous interventions. RCT should compare the outcomes described, overall morbidity, disability, comorbidities, recurrence, and safety (therapy-related side effects).

Two investigators independently searched the literature in February 2022 in PUBMED (Medline), LILACS, SCOPUS, EMBASE Cochrane Central Register of Clinical Trials and Grey Literature with no limitations to identify with the selected PICO strategy, and Mesh terms derived ((((“sickle cell disease”) OR “anemia sickle cell”) AND “priapism”) AND “management”). This research was posteriorly limited to results of “Medicine” studies that included humans, and articles, published in English or Spanish. The CONSORT strategy was selected and used for carrying on the study.

Data from studies that accomplished the inclusion criteria filter were extracted independently by three authors. Any discrepancy found was resolved between the first two authors, if there were consensus discrepancies, the third author opinion was included in the study.

Technical information

This systematic review responds to the PICO question that aims to define if the management interventions in All-type priapism in SCD patients are equally effective in reducing overall morbidity, disability, comorbidities, recurrence, and safety (therapy-related side effects) and includes the definition of the impact of interventions on reduction of recurrence of priapism crisis, ischemic transformation crisis; reduction of therapy-related side effects, or safety differences; define assessment methods in the entity; and defining if there are non-assessed outcomes in studies for management in this population.

For each study, evaluation of bias risk was individually done, using Cochrane Bias analysis strategy. Five categories were considered and analyzed, classified in high, low, and not defined:

- Selection Bias: determining if the sample was representative, generation of an assignment sequence, and Blind design of the study. Randomized sample, and independence of the sample
- Experimenter expectancy bias: determining Blind Design of the studies
- Measurement Bias: determining gathering of information distortion, placebo-control groups
- Report Bias: comparison of outcomes described in methods versus in results
- Lead time Bias: determining if there are individuals without follow-up. Severity stratification.

Statistics

If studies were comparable, the analysis of the effect and intervention odd ratios was used of dichotomous outcomes, and hazard ratio when information of incidence density. Heterogeneity was assessed from a clinical point of view and a statistical method applying I square calculation (heterogeneity %) (Review manager 5.2), if it was > 50% among studies, analysis of the main source was addressed (Population, intervention differences, and outcomes measurement). A sensitivity analysis was performed. For all analysis, a confidence interval of 95% was taken as reference.

If the studies were clinically and statistically homogenous, studies combination using the inverse variance fixed-effects, visual exploration with Forest Plot of Quantitative Data and Statistical Cochrane Calculation, Null hypothesis assuming homogeneity, was prospected.

Results

Studies characteristics and assessment

The research strategy is shown in figure 1. Twenty-one titles identified with different interventions and designs, 19 eligible articles, 10 removed after full-text reading due to design that did not fulfill inclusion criteria (Table 1). Nine studies included were published between 1996 and 2014 (Table 2).

A qualitative analysis based on clinical heterogeneity of the studies, characteristics (Table 3.1), and outcomes (Table 3.2) was done based on PRISMA guidelines. Studies were not comparable based on their interventions approach, were clinically heterogeneous, no statistical analysis was done.

Seven were case series, and two were randomized controlled Trials. Two texts had random designation of the intervention, one had a blinding strategy in the participants (Baby-Hug, 2011), one with control group which received the same intervention as the other group. The average time of follow-up was 17.4 months, with a range between 10 and 37.15 months (Table 4). Most of them had no method for calculating sample size, with an average of 33 patients. A total of 300 patients were included in the qualitative analysis. Four took place in the United States, two in Brazil, and one in each: Togo, London, and France. The average age was influenced by the inclusion or exclusion of pediatric patients and the size of the sample, noticing a positive association between them, the bigger the sample, the more patients in pediatric age. Intervention and technique are shown in Table 4.

Table 1. Excluded studies

Author, year	Removal reason
Hoeh, 2014	Retrospective review and a phone survey of 17 patients with RIP were performed
Konstantinos, 2009	Review. No intervention
Lane, 2011	Case report, 1 case
Howard, 2013	No priapism as an outcome
Lottenberd, 2005	Review. No intervention
Marque, 2011	Review. No intervention
Olojohungbe, 2013	Review. No intervention
Teloken, 2005	Case report, 1 case
Voskaridou, 2010	No priapism as an outcome
Wang, 2016	Retrospective study

Outcomes analysis

Comorbidity

Not included in studies. Many perspectives could be drawn considering pathophysiology.

Morbidity and recurrence

Morbidity is associated with frequency of episodes, recurrence, and quality of life of the patients. The frequency of the episodes was the main outcome; however, the sample size is a limitation for making conclusions from the statistical analysis reported in studies.

For each type of intervention, relationship conclusions, but not causality can be done; for finasteride, chronic control medium dose (3 mg) generate promising results; however, comparing two studies included with this intervention, both had statistically significant results even though one used lower doses. For PDE-5 inhibitors, two case series were included, despite the author and research group being the same, the result of the second is unclear, it could have impact in erectile function preservation, more studies should be done for finding significant risk reduction.

For Oral etilefrine and acute episode control with injections, four studies were included in the study, duration, recurrence, erectile function, and detumescence were assessed. Although outcomes were differently approached and may not be compared, this intervention is promising.

Duration of episodes was not reported, the nature of this outcome should be measured in a standardized way that was absent in studies.

Adverse effects. Therapy associated outcomes

Are shown in tables 3.1 and 3.2, causality relationships may not be done.

Quality of life

Not assessed, any score for the follow-up of the interventions included in the study.

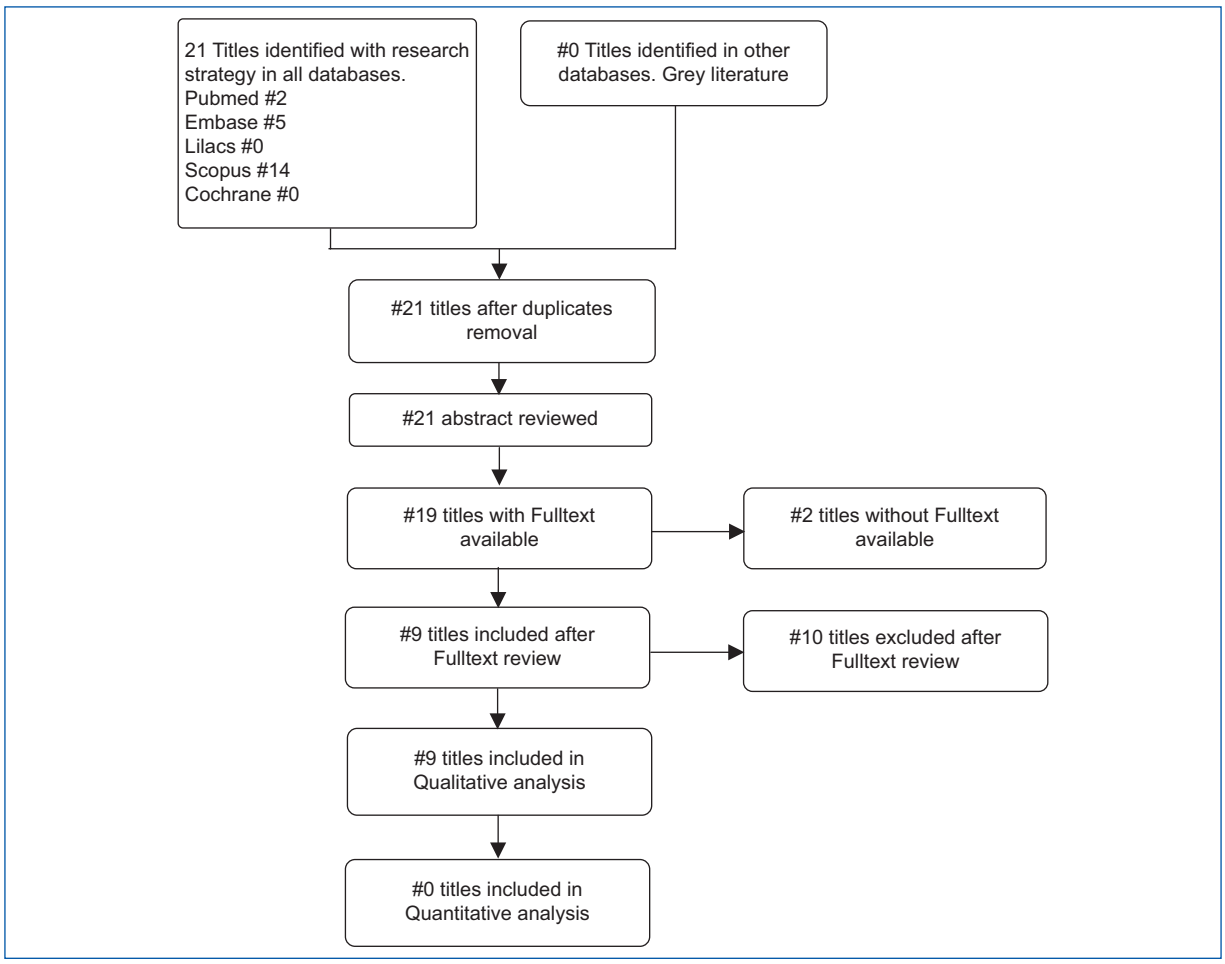

Figure 1. Flow diagram (Developed with REVMAN 5.4 platform)[36].

Table 2. Included studies

Author, year	Intervention	Type of study
Baroso, 2012	Finasteride 1 mg once or twice a day	five cases, prospective. No control. Case Series, 4 years
Burnett, 2006	Short action PDE5 inhibitor, sildenafil 25 mg daily	3 SCD cases, prospective. No control. Case Series
Burnett, 2014	Short action PDE5 inhibitor, sildenafil 50 mg daily 8 months	RCT, two phases
Gabdoe, 2001	Etilefrine 0.25 mg/kg 1 time a day, 1 month	11 SCD cases, prospective. No control. Case Series
Mantadakis, 2000	Etilefrine Intracavernous injections 10 mL of 1:1000000 sol. Chronic control of chronic follow-up w Oral pseudoephedrine or IM leuprolide	15 SCD cases, prospective. No control. Case Series
Okpala, 2002	Etilefrine Oral 25 mg/daily AP (6-10 mg Intracavernous injection etilefrine)	18 SCD cases, prospective. No control. Case Series
Rachid, 2009	Finasteride, 4 phases 5 mg day or 3 mg day or 1 mg day	35 SCD cases, prospective. No control. Case Series, 5 subgroups taking into account recurrences number
Virag, 1996	Etilefrine Oral 15 or 30 mg day, AP Self injected Etilefrine 0.6 mL of 10 mg/mL sol)	6 SCD cases, prospective. No control. Case Series
Baby Hug, 2011	Hydroxycarbamide, 20 mg/kg/day for 2 years	RCT, Double Blind

SCD: Sickle cell disease.

Table 3.1. Studies summary

Study (Author, year)	Location	Intervention	Sample size	Elegible criteria	Outcomes	Follow-up time (mean/ months)	Complications/ recurrence
Okpala et al., 2002	Department of Haematology, St. Thomas' Hospital, London, UK	Etilefrine Oral 25 mg/ daily AP (6-10 mg Intracavernous injection etilefrine)	Total (n): 18 Average age: Not reported 1st time (n): 0 Recurrent (n): 18	Children and adolescents with recurrent episodes of priapism	Detumescence: Not assessed Erectile Function: Not assessed Duration of episodes: Recurrence (frequency of SP) M 5.78 (SD) 0.99 p < 0.0001 Reduction of severity M 1.72 SD1.21 p < 0.0001	14.7	Complications: Blood pressure Impairment 0/18 0%
Rachid et al., 2009	Souza Aguiar Municipal Hospital, and Urogenital Basic and Translational Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil	Finasteride, 4 phases 5 mg day or 3 mg day or 1 mg day	Total (n): 35 Average age: Not reported 1st time (n): 0 Recurrent: (n): 35	SCD with recurrent episodes of priapism in finasteride treatment alone	Detumescence: Not assessed Erectile Function: Not assessed Duration of episodes: Frequency of episodes between days of treatment/D1- 40 M 10.7 SD 3.9 p < 0.0001/040-80 M8.2 SD6 p < 0.0001/ D80-120 M1.5 SD4.3 P0.025 (Four phases-Doses)	11	Complications: Painless Gynecomasty 6/35 patients 17%
Virag et al., 1996	Centre d'Explorations et de Traitements de l'impuissance, Paris, France, and Sickle Cell Center Policlinic, Hopital H. Mondor, Creteil, France	Etilefrine Oral 15 or 30 mg day, AP Self-injected Etilefrine 0.6 mL of 10 mg/mL sol)	Total (n): 6 Average age: range 22-31 years old 1st time (n): 0 Recurrent (n): 6	Adults with SCD recurrent episodes of priapism	Detumescence: Not assessed Erectile Function: Unchanged in 5/5 100% Duration of episodes: Not assessed	13	Complications: Blood pressure impairment 0/6 0%
Baby Hug et al. 2011	Jhons Hopkins Hospital, Baltimore, USA	Hydroxycarbamide, 20 mg/kg/day for 2 years	Total (n): 193 Average age: Not reported First Time: Not estimated Recurrent: Not estimated	13 central recruitment, Hbss or thalassemia	Detumescence: Not reported Erectile Function: Not reported Duration of episodes: Not assessed Frequency of priapism: Priapism episodes as Secondary outcome, TMT N4 events PT 3% (SD) PCB N2 events PT2 P0.67	18	Complications: Not assessed

Table 3.2. Studies summary

Study (Author, year)	Location	Intervention	Sample size	Elegible criteria	Outcomes	Follow-up time (mean/ months)	Complications/ recurrence
Baroso et al., 2012	Escola Bahiana de Medicina e Saúde Pública, BA, Brazil	Finasteride 1 mg once or twice a day	Total (n): 5 Average age: 10.6 years old 1st time (n): 0 Recurrent (n): 5	Children and adolescents with recurrent episodes of priapism No-SCD patients excluded	Detumescence: Not assessed Erectile Function: Impaired 0% Duration of episodes: Not assessed Death: Not assessed	20	Complications: not assessed Recurrence: During (n) 3-60% After (n): 1-20% Frequency of episodes: Not reported
Burnett et al., 2006	James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland	Short action PDE5 inhibitor, Sildenafil 25 mg daily	Total (n): 4, 3 SCD Patients Average age: Not reported 1st time (n): 0 Recurrent (n): 4	Patients with SCA-related recurrent episodes of priapism (No age limitations)	Erectile Function: Preserved in all patients Duration of episodes: Reduction in all patients	10	Complications: Not assessed
Burnett et al., 2014	James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland	Short action PDE5 inhibitor, Sildenafil 50 mg daily 8 months	Total (n): 13 Average age: Not reported 1st time (n): 0 Recurrent (n): 13	Patients with SCA-related recurrent priapism (> 2 times)	Detumescence: Not reported Erectile Function: Not assessed Duration of episodes: Frequency reduction 50%, Phase 1 ITT TMT 3/6 (50%) vs. PCB 3/7 (42.9%) P0.1 / PP 1/3 33.3%. 2/4 50% P1.0	4	Major priapism episodes during actively sildenafil/ placebo
Gabdoe et al., 2001	Division of Infectology and Onco-hematology, Department of pediatrics, University of Lomé, Lomé-Togo	Etilefrine 0.25 mg/kg 1 time a day, 1 month	Total (n): 11 Average age: 13 years old 1st time (n): 6 Recurrent (n): 5	Children and adolescents with recurrent episodes of Sluttering priapism and Acute priapism	Detumescence: Not reported Erectile Function: Not assessed Duration of episodes: No relapse 6/6 (1st time), Remission 3/5 60%, Cure 1/5 20%	28.9	Complications: Agitation in 1/11 patients 9%
Mantadakis et al., 2000	Department of Pediatrics, 5323 Harry Hines Boukevard, Dallas TX	Etilefrine intracavernous injections 10 ml of 1:1000000 sol. Chronic control of chronic follow up w Oral pseudophedrine or IM leuprolide	Total (n): 15 Procedures (n): 39 Average age: 13.7 years old 1st time (n): 2 Recurrent (n): 13 (3.9-18.3) (86%)	Patients with Homozigous SCA with SCA related priapism, that failed general measures stablished in protocol or episode lasted longer than 2 h, that seek medical attention at the emergency room of the Children´s Medical Center of Dallas	Detumescence: < 1 min 37% Efficacy: 95% CI (81-99%) Erectile Function: Impaired 2/13 15% Duration of episodes: Not assessed Death: Not assessed	35.15 (39, only 7, > 18)	Complications: Penile hematoma 2/39 5% (13% of patients)

Table 4. Interventions summary

Author	Intervention	Dose	Interval	Crisis management	Time of chronic/ prophylaxis management (months)	Time of follow up (mean /months)
Baroso	Finasteride, Oral	1 mg	q.d or b.i.d	Hydratation and Drainage	7.5 ± 3	20
Burnett	Sildenafil, Oral/ Tadalafil, Oral	25 mg-5 mg	q.d/q.d	Hydratation, aspiration, irrigation	N.S	10
Burnett	Sildenafil, Oral	50 mg	q.d	N.S	8	16
Gabdoe	Etilefrine, Oral	0.25 mg/kg	q.d	Etilefrine 5 mg IC Injection	1	28,9
Mantadakis	Etilefrine, Intracavernous	Injections 10 mL of 1:1000000 sol.	In acute priapism	Etilefrine Injections 10 mL of 1:1000000 sol.	Oral pseudoephedrine or IM leuprolide	37.15 (39, only 7, > 18)
Okpala	Etilefrine, Oral	25 mg/kg	q.d	Etilefrine 6-10 mg IC injection	14.7	14.7
Rachid	Finasteride, Oral	5 mg or 3 mg or 1 mg	q.d	-	4	11
Virag	Etilefrine, Oral	15 mg or 30 mg	q.d	Self injected Etilefrine 0.6 mL of 10 mg/mL sol)	4	13
Baby Hug	Hydroxycarbamide	20 mg/kd	q.d	-	14	18

Table 5. Bias analysis, summary

Baroso, 2012	-	-	-	?	?
Burnett, 2006	+	-	-	+	?
Burnett, 2014	+	-	-	-	-
Gabdoe, 2001	-	-	-	+	-
Mantadakis, 2000	?	-	-	?	+
Okpala, 2002	-	-	-	+	+
Rachid, 2009	+	-	-	?	+
Virag, 1996	?	-	?	?	+
Baby Hug, 2011	-	+	-	?	?
BIAS TYPE	SECTION	EXAMINEER EXPECTATION	MEASUREMENT	REPORT	FOLLOW-UP

Bias analysis

Table 5 resumes the five spheres of bias that were analyzed for each study.

Most studies had a high risk of bias associated with examinee's expectation, lack of blinding strategies and of standardized scores for evaluating frequency, and erectile function. Three studies included pediatric patients or recurrent priapism without having SCD as a main inclusion criteria. The follow-up was insufficient for some outcomes like erectile function and quality of life.

Discussion

There are no meta-analysis or systematic reviews associated with SCD-related priapism. This is the first approach to information analysis associated with this complication. There are several comprehensive treatment guidelines based on individual management, or specific institution's experience[9]. European guidelines give the most valid and accurate approach; however, most recommendations are based on expert consensus and are non-specific for SCD patients[10].

Our intention for this systematic review was having evidence-based information for this specific population taking into account the prevalence of SCD in our country, Colombia[37].

Pharmacological treatment of SCD-related priapism, should be addressed and have promising results, having chronic control, and less surgical-related ED; however, the method and designs of the studies related to this population and conditions are limited.

Etilefrine, intracavernous injections, and oral management could be a strategy for including in specific guidelines for patients with recurrent priapism. No causality could be concluded, perspectives are clearly produced.

Conclusion

This is the first information analysis approach for a treatment consensus of SCD-related priapism. The main perspective is the need of studies with internal validity and elaborated designs for further causality relationships and evidence-based approach to this condition. Quality of life scores should be evaluated and could be the main outcome for deciding the best intervention alternative.

Molecular studies should play a role in generating further perspectives in understanding the pathophysiology of SCD-related priapism, and molecular studies-based strategies for chronic control and recurrence prevention.

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Conflicts of interest

Authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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