

Extracorporeal lithotripsy in patients with hemophilia: systematic review.

La lithotripsie extracorporelle en hémophilie : revue systématique de la littérature.

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RÉSUMÉ

Prérequis : La prise en charge des lithiases urinaires chez des patients hémophiles pose un vrai défi pour l'urologue.

But : Evaluer la sécurité et l'efficacité de la Lithotripsie Extracorporelle (LEC) dans le traitement des lithiases urinaires chez les hémophiles.

Méthodes: Une revue systématique a été réalisée en se référant au moteur de recherche de la National Library of Medicine (PubMed) entre Janvier 1985 et Juin 2013 et en utilisant ces mots clés: "Hemophilia" and "extracorporeal shock wave lithotripsy". Tous les articles portant sur le traitement des lithiases chez les patients atteints d'hémophilie par la LEC ont été inclus. Deux examinateurs ont extrait les données de chaque étude. Ces données ont été analysées et discutées.

Résultats: Au total, 12 articles médicaux ont été retenus avec un total de 25 patients. La taille des lithiases variait de 6 à 21 mm. La substitution des facteurs de coagulation déficients a commencé la veille de la LEC. La LEC était efficace chez tous les patients sauf un après 1-6 séances/patient. Une échographie a été réalisée après la procédure afin de chercher des complications hémorragiques potentielles. L'arrêt du traitement substitutif dépendait de l'état général du patient, la présence d'hématurie et l'absence de signes d'hémorragie. Des complications hémorragiques majeures ont été observées chez 4 patients.

Conclusions: Avec une substitution efficace des facteurs de coagulation déficients, la LEC est une méthode sûre et peu morbide dans le traitement des calculs urinaires chez les hémophiles

Mots-clés

Calcul urinaire, Lithotripsie extracorporelle, Hémophilie A, Hémophilie B, Inhibiteur du facteur VIII, Trouble de coagulation.

SUMMARY

Background: The management of urolithiasis in patients with haemophilia poses a real challenge to the urologist.

Aim : We conducted a systematic literature review to assess the safety and efficacy of extracorporeal shock wave lithotripsy (ESWL) in the treatment of urolithiasis in hemophiliacs.

Methods: A systematic review was conducted by using the National Library of Medicine (PubMed) search engine between January 1985 and June 2013. We've used these key words: "haemophilia" and "extracorporeal shock wave lithotripsy". All articles dealing with the treatment of nephrolithiasis by ESWL in patients with hemophilia were included. Two independent reviewers extracted the data from each article. The data was included into a systematic review and analyzed.

Results: A total of 12 medical articles were selected with a total of 25 patients. The stone size varies from 6 to 21 mm. The substitution of the deficient clotting factor started the day before the ESWL. ESWL was effective in all patients except one after 1-6 sessions / patient. An ultrasound was performed after the procedure to look for potential bleeding complications. The judgment of the substitution therapy depends on the patient's condition, the presence of hematuria and the absence of signs of bleeding. Major bleeding complications were observed in 4 patients.

Conclusions: With effective substitution of deficient clotting factors, ESWL is a safe and low morbidity method in the treatment of urinary calculi in hemophiliacs.

Key - words

Urinary calculi, extracorporeal shock wave lithotripsy, haemophilia A, haemophilia B, factor VIII inhibitor, coagulation disorders.

Since the development of extracorporeal shock wave lithotripsy (ESWL) and its introduction to clinical practice, it became the standard in treating renal and proximal ureteral stones. Nowadays, pregnancy and decompensated coagulation disorders are thought to be the only residual contraindications to ESWL (1). Hemophilia, the most severe congenital hemorrhagic disorder, is due to deficiency of VIII (hemophilia A) or IX (hemophilia B) plasma coagulation factor (2). This condition makes the surgical management of patient with urological disorder complex and risky. Brown had reported 8% of deaths in hemophiliacs in general surgery (3). However, several papers emphasize the possibilities of urological surgery in these patients, especially in no urgent conditions, by accomplishing correct biological and surgical hemostasis until healing is achieved (4-6).

Owing to a general tendency in urology to limit the indications for surgical treatment of urolithiasis, attempts were made to apply ESWL (7-9) in these patients. The risk of hemorrhagic complications with this procedure rises considerably among them, therefore, such treatment requires careful and correct substitution of the deficient coagulation factor (7,10,11).

In view of all the related literature, we aimed to conduct a systematic review to assess the safety and efficacy of ESWL in haemophiliac patients. The special risks and alternatives to blood product therapy are reviewed.

METHODS

A systematic review of the contemporary urological citations was conducted using the National Library of Medicine (PubMed) search engine. The search strategy was conducted to find relevant studies from MEDLINE (1985- June 2013). Search terms used included: "Hemophilia" and "extracorporeal shock wave lithotripsy".

We included only papers that discussed original series or case reports dealing with urolithiasis in hemophiliac patients treated by ESWL. All

articles, whatever was the language, was included. Wherever data was not available or not enough clear in the reports, lead authors were contacted to provide the raw data. Articles with final poor information about patients or treatment were not included. Two independent reviewers extracted the data from each article. The data was included into a systematic review and analyzed.

The following variables were extracted from each study: Period of the study, population demographics (patient age, gender, presenting symptoms), type of hemophilia and its severity, stone characters, post-ESWL complications and stone free rates.

The demographic data are presented in Table 1. These data were grouped into a systematic review to allow a numerical representation of the results. It is intended that this will serve as a reference for practicing urologists, enabling them to be aware of the special explorations and preparation of hemophiliac patients with urolithiasis.

RESULTS

Literature searches:

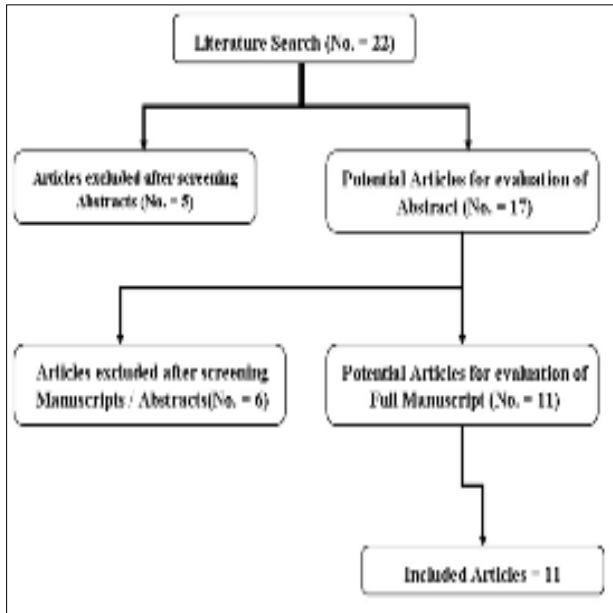
The literature search yielded 22 studies, Five of them were excluded by title or abstract for non-relevance to the aims of this review and two because expressive patients' data were not available, the authors had not provided demographic, hemophilia type, or stone details separately for these patients and therefore could not be extracted. Attempts at contacting the author were unsuccessful. Thus, we examined 11 full manuscripts only (Figure 1)(1-2,7-15). We added to this review one patient managed in our department and another one reported in a related article (16).

All the studies were published between 1986 and as recent as 2003, reflecting the continued debate of ESWL indication and safety in treating stones in hemophiliac patients.

All studies were retrospective and include only one series (2).

Table 1 : Demographic data

Author	Hemophilia type	Presenting symptoms	Stone location	Stone size
Czaplicki M (2)	Severe hemophilia A: 7 Mild hemophilia A: 1 Severe hemophilia B: 3	-	Kidney: 9 Ureter: 1 Kidney and ureter: 1	7 x 6 ⇒ 21 x 15
Montanari E (11)	Severe hemophilia A Severe hemophilia A	Renal colic/ Hematuria Fever / Hematuria	Renal pelvis Renal pelvis + ureter	10 x 5 6 x 5.5
Leusmann DB (13)	Severe hemophilia A	Hematuria	Kidney	-
Brunet P (12)	Hemophilia B	No hematuria	Renal Pelvis	-
Christensen JG (10)	Mild hemophilia A	-	Kidney	13 x 9
Becopoulos T (1)	Severe hemophilia A Mild hemophilia B	Renal colic	Kidney Renal pelvis and pelvi-ureteric junction	- -
Partney KL (7)	Severe hemophilia A	Renal colic	Kidney	18 x 10
Alvarez JA (8)	Mild hemophilia A	Fortuitous	Renal pelvis	-
Economacos G (9)	Hemophilia B	-	Kidney	-
Mataix Corbi R (14)	Severe hemophilia A	-	-	-
Lauper M (15)	Hemophilia B	-	-	-
Our case	Hemophilia A	Renal colic	Renal pelvis	17 x 11
Ghosh K (16)	Minor Hemophilia A	Hematuria	Renal pelvis + lower calyx	17 + 6

Figure 1: Flowchart for article selection process of the review**Characteristics of the included studies:**

This systematic review accounts 25 haemophilic male patients who underwent at least 39 procedures. The age ranges from 22 to 68 years with a mean of 44.1 years.

All patients had confirmed hemophilia including 18 patients with hemophilia A and 7 with hemophilia B (severe hemophilia in more than half patients). The diagnosis of hemophilia was made during the preoperative assessment in all cases but one (8). None of the patients had another associated coagulopathy or under treated with antithrombotic agents. Macroscopic hematuria was the most frequent presenting symptom. The stone sizes ranged from 6-21 mm with predominance of renal stones.

All the subjects, but one (8), were managed with collaboration of the hematology department.

Platelet count and the prothrombin time were well within normal limits in almost all cases. High titre of factor VIII was reported in 4 patients (2,13) and screen for inhibitor was negative in 5 patients (7,10,11,16). Substitution therapy was started the day of or one day before the procedure and was conducted up to 21 days. Substitution therapy protocols were very different: bolus, infusion, doses. Two patients didn't receive deficient factor because one of them was not known as haemophilic (8) and the other refused this substitution therapy considering it too risky (10). The 25 hemophiliacs underwent at least 42 sessions of ESWL (1-6 / patient). No incident was mentioned during the procedure. The duration of post-treatment substitution varied from author to another (1-21 days) and depended on the patients' general status, the presence/absence of hematuria and the results of ultrasound or computed tomography examination (2). Substitution withdrawal was based on the patients' good general status, lack of hematuria and absence of signs of hemorrhage.

Eight patients had skin ecchymosis at the site of contact with the lithotripter head. Only – patients developed short, minor hematuria

after ESWL. Major hemorrhagic complications were found in only 4 patients (8,14,15): haemorrhagic shock in two patients and perirenal hematoma in two patients necessitating renal artery embolization. Noting that one haemophilic patient with haemorrhagic shock was a fortuitous discovery (8). These major complications were reported in patients managed between 1986 and 1994, however, no serious complication was reported after that date. Transient macroscopic hematuria, which lasted for 1-3 days, was observed after the procedure in five patients but did not require any specific management (7,9-11 and our's).

Failure was reported in one patient after 2 sessions of ESWL on the same stone (1), stone recurrence was report by one author (13) after 1 year of follow-up and residual stone were noted in 5 patients (2,11,12). The stone free rate was as high as 82%.

DISCUSSION

This systematic review found that the use of ESWL on haemophilic patients is not only safe but also efficient, with an overall stone free rate of 82%, a minor bleeding complication rate and a major complication rate of 13% (since 1994 no major complication was reported).

With appropriate perioperative monitoring and therapy, as recommended by a consulting hematologist, patients with hemophilia may undergo ESWL as indicated by their stone disease (10). Taking into account the minimal invasiveness of ESWL, we think it should be considered as a method of choice urolithiasis management in hemophiliacs (2,17) as in normal patients. ESWL is no more an absolute contraindication for hemophiliacs. Two conditions should be considered: close cooperation with a specialized hemophilia center with hematological facilities and administration of proper substitution therapy (1,2,9).

The hemophilia A (factor VIII deficiency) and B (factor IX deficiency) may be severe (rate of loss factor less than 1%), moderate (factor deficiency rate between 1 and 5%) or mild (rate factor deficiency between 6 and 40%) (5). Severe and moderate hemophiliacs have often hemorrhagic manifestations that have been wearing the diagnosis before the onset of urological disorders (5). However, moderate or mild haemophilia are usually discovered with the preoperative assessment. Although, haemophilia patients are predisposed to renal stone formation, this condition has rarely been reported in the literature apart from isolated case reports.

Since 1980, the ESWL has become the gold standard option for treatment of renal and ureteral calculi. Advancements in ESWL lithotripter engineering allow managing stones in the whole upper urinary system, including the renal calyces and proximal ureter with a very low reported long-term complication rate.

The most frequent effect of ESWL is hematuria due to microtrauma and microscopic hemorrhage in normal kidneys (18). Clinically significant hemorrhagic complications following ESWL occur in 0.3-0.6% of normal patients without coagulation disorders (8,10). The risk of perirenal or intrarenal hematomas is estimated to be between 0.1% and 0.6% with ultrasonography (19) and between 19% and 29% with MRI or CT Scan imaging (8,18,20,21). These rates of hemorrhagic complications after ESWL vary depending on the type of machine: 0.2%-0.66% (19) with a hydroelectric lithotripter type Dornier, 2.5%

with piezoelectric lithotripter (22) against 27% to over 50% for hydroelectric lithotripter type KNAPP (19). For these reasons, congenital and acquired defects of hemostasis were considered an absolute contraindication to ESWL treatment. But over the years, several patients with disorders of hemostasis have been treated successfully (Table I).

Normalizing coagulopathy pre-operatively is the mainstay of patients' management before ESWL procedure. This usually leads to the combined consult and coordinated efforts of the urologists with the haematologists and anaesthetists. It is a crucial step of stone management, hypovolemic shock after ESWL in a case of unrecognized hemophilia has been described (8).

There is no consensus of opinion as to what should be the minimum safe factor VIII or IX levels in hemophilia patients during the operative or post-operative period. It is also not known how long this level has to be maintained. It is reasonable to continue the haemostatic level until the healing process is well under way (16). Brown (3) suggested that the factor level should be raised to 100% of normal before the operation and a level greater than 50% of normal should be maintained for 2-7 days surgery.

Preoperative preparations with full or shortened substitution were proposed. Infusions of 3,500-13,000 units during 1-3 days have been reported also (1,7). Christensen et al. (10) presented a patient, with mild hemophilia A, who refused pre-ESWL treatment with Factor VIII concentrate or cryoprecipitate because of the fear of contracting acquired immunodeficiency syndrome (AIDS) or hepatitis. He was treated without complications and with no substitution at all.

The presence of antibodies with anticoagulant effect should always be sought in the preoperative assessment of hemophiliac, because they make it difficult or even impossible to obtain plasma hemostasis (2,5).

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Treatment with activated prothrombin complex concentrate (APCC) results in an improvement of coagulation by bypassing the deficient factor (23). Becopoulos et al (1) propose, in patients with haemophilia, a smaller dose and shorter duration of substitution therapy with ESWL compared to that of open surgery. This is of great importance not only because of the low cost of the procedure but also because it minimizes the danger of side effects especially the infusion of high quantities of concentrates (1). Thus using these preconditions, ESWL can safely be recommended for these patients (13,24).

Pre- and post-treatment care should take place in a hospital ensuring continuous hematologic and urologic care and not as an ambulatory procedure. The lack of hemorrhagic complications on ultrasound examination, regression of hematuria and the patient's good general status are sufficient criteria for substitution withdrawal after the procedure (2). This systematic review has many limitations related to the patient population (25 patients only) and the lack of some data. Thus, we did not see a need of conducting sub-groups analysis which would have reduced the cohort even further. Despite these limitations, grouping of the data was possible and revealed the safety and efficacy of the procedure. Furthermore, this review opens possibility for further research into the question.

CONCLUSIONS

Through this literature systematic review, we concluded that ESWL is a safe and efficient procedure in hemophiliacs, providing that substitution therapy to correct coagulation disturbances is adequately administered (Grade B recommendation) in very close collaboration with haematologists. As a consequence ESWL should be considered as a method of choice in adequate cases (Grade C recommendation).

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