USING VERAPAMIL AS PROTECTIVE FACTOR IN RENAL ISCHEMIA REPERFUSION INJURY DURING ANATROPHIC NEPHROLITHOTOMY

Damir Aganović*, Benjamin Kulovac, Alden Prcić, Osman Hadžiosmanović

Urology Clinic, University of Sarajevo Clinics Centre, Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina

* Corresponding author

Abstract

Anatrophic nephrolithotomy (ANL) in the selected cases represents the method of choice in the treatment of staghorn calculi. We evaluated postoperative outcome of patients subjected to standard ANL that received 10 mg of Verapamil immediately before declamping renal artery, due to prevention of reperfusion injury. From 2002 to 2005, 18 nephrolithotomies were performed on 15 patients, in the Urology Clinic, University of Sarajevo Clinics Centre. Preoperative evaluation included intravenous urography and radionuclide renal scans which had been repeated 6 months after the operations. 10 males and 5 females were operated with mean age of 45 years. Urography and renal scans showed severe calyceal distortion and infundibular stenosis in 83% cases, complicated with ureteropelvic junction obstruction in 55% cases. Chronic kidney failure was present in 60% patients. Mean operative time was 150 minutes, with mean cold ischemia time of 61 minutes and mean blood loss of 300ml. There were five minor postoperative complications. Residual small calculi were found in 3 patients. Kidney function was stabilized in the patients suffering from chronic kidney failure, which was proved by radio nuclide imaging. ANL improved by using calcium channel blockers as a protective factor for reperfusion injury proved to be a good treatment choice with a low level of complications and noticeable stabilization and improvement of kidneys function.

KEY WORDS: staghorn stone, anatrophic nephrolithotomy, prevention of reperfusion injury

Introduction

Staghorn calculi are stones that fill the major part of the renal collecting system. They occupy the renal pelvis and branch into most of the calyces (1, 2). If they are left untreated, it leads to an inevitable loss of kidney function and results in up to 28% mortality rate (2). Conservative treatment of these stones also leads to complete renal failure. Staghorn stones are usually struvite stones, composed from magnesium, ammonium and phosphate, mixed with carbonate (3). Infections with urea-splitting bacteria and residual urine (4) as the result of anatomic abnormalities (infudibular stenosis, calyceal distortion and ureteropelvic junction obstruction) are the main cause of creation of these stones. Therefore, the main goal in the treatment is a complete removal of the stones and treatment of the etiological cause. The basic open surgery procedure is the ANL. It was developed in late 60s of the last century. The first one was performed by Smith and Boyce in 1967 (5). This method gained popularity by using local renal hypothermia (superficial ice-slush cooling of the kidney) to decrease rapidly metabolic activities and preserve renal function of anoxic phenomena during the temporary occlusion of the renal artery (6). Due to metabolic changes during renal ischemia and cooling of the kidney, there is a relative risk for renal cells to suffer from reperfusion injury (7). To overcome this problem we introduced intravenous administration of 10 mg of Verapamil just before declamping the renal artery, which is in accordance with the renal transplant practice (8).

Material and Methods

During the period 2002-2005, 18 nephrolithotomies in local hypothermia were performed on 15 patients, (3 patients suffered from bilateral disease, one combined with stone in the urinary bladder), in the Urology Clinic, University of Sarajevo Clinics Centre. Two patients were paraplegics, one had solitary kidney burden with staghorn stone. Preoperative evaluation included detail medical history and clinical examination, which showed that the majority of patients had flank pain, urinary infections, lower urinary symptoms, loss of appetite and recurrent fever. The following analyses were done: serum creatinine and BUN, glomerular filtration rate (GFR), urine cultures, as well as radio nuclide imaging (technetium m99 DMSA and DTPA renal scan). All the patients who did not have advanced renal failure were further examined by intravenous urography (IVU) (12/15). All the tests were repeated 6 months after the operations. The complete hormonal investigations were mandatory for every patient. Preoperatively all patients were treated with third generations of cephalosporin. The surgical approach was lumbar, over eleventh rib with its resection. Standard ANL in local hypothermia was used. Superficial cooling of kidney aimed at decreasing the core temperature below 20 Co (9) to reduce renal metabolic activity and its need for oxygen supply. Prior to artery declamping, every patient received iv.10 mg of verapamil (8) and 20 mg of furosemide to prevent reperfusion injury. All patients were stented.

Results

10 male (75%) and 5 female (25%) patients were operated. Their mean age was 45 with the range between 22 and 65 years. Mean preoperative follow-up was 25 months. Preoperative interventions were made on six patients (40%): three failed ESWL treatments, two previous kidney operations and one treated urinary sepsis. Urinary infection was present in 12 patients (80%) with dominant *Proteus* and *Pseudomonas bacteria*. IVU combined with technetium m99 DMSA and DTPA renal scan showed severe calyceal distortions and infundibular stenosis in 83% of the total number of kidneys complicated with obstruction of ureteropelvic junction (PU) in 55% cases. 9 patients (60%) suffered from chronic renal failure (3 of them with an advanced stage), while metabolic disorder was present in two patients (13%) - cystine lithiasis and hyperparathyroidism (Table 1). Average operation time was 150 minutes with mean cold ischemia time (CIT) of 60, 6 min. Calculated mean blood loss was 302 ml (Table 2). There were three minor intraoperative complications (venous back bleeding) which requested supplementation with average two fresh blood units per patient. Early minor postoperative complications were observed after five operations (28%). Three cases (17%) had prolonged intrapelvic hemorrhage, which was treated conservatively with transfusions, while wound infections appeared after two operations (11%).

Observed characteristics	No	Percent
Urinary infection	12/15	80%
Preoperative intervention	5/15	33%
Infundibular stenosis	8/18	44,4%
Calyceal distortion	15/18	83,3%
PU junction obstruction	10/18	55%
Chronic renal failure	9/15	60%
Metabolic disease	2/15	13,3%

TABLE 1. Preoperative conditions

Observed characteristics	Mean	Min.	Max.	Median
Age of the patient	45,3±3,2	22	66	49
Preoperative follow up (months)	25±4	3	64	20
Postoperative follow up (months)	19,3±1,8	9	32	19
Preoperative creatinine (μmol/L)	162,1±28,7	84	520	113,5
Operative time (min)	149,5±5,5	118	195	144
CIT (min)	60,6±1,9	45	77	61
Calculated blood loss (ml)	302,8±34,5	100	800	27,5
Number of blood units	2,1±0,5	1	4	2

TABLE 2. Characteristic specific to the operations

The main stone composite was struvite in 12 patients (80%), hydroxiapatite stones were found in 2 patients (13%), and one patient had cystine lithiasis (7%). Residual calculi less than 1 cm were found in 3 kidneys (17%) and recidive of lithiasis (diagnosed after prolonged follow up) in three patients (20%). These cases were successfully treated with ESWL. Only two patients harbored urinary infection in postoperative period (13%).
Global renal function was stabilized in 9 patients with chronic renal failure, while it was improved in the patients with no renal failure (proved by GFR, serum creatinine, BUN and control renal scans). Serum creatinine dropped from mean preoperative value of 239 μmol/L to mean 190 μmol/L (p=0, 02).

Discussion

Although ANL represents relatively good therapeutical choice in the treatment of patients with staghorn calculi, it is considered as an old fashioned procedure. Advantages of endoscopic and percutaneous procedures combined with ESWL are the same stone-free rate with less intraoperative complications, less morbidity, faster recovery and less hospital stay. Furthermore, one of the most important advantages of these minimal invasive procedures is that there is no need for renal hypothermia and kidney ischemia (1).

Cold ischemia, which is simple and relatively safe method for kidney preservation, bears a risk of reperfusion injury of renal cells. With ischemia, ATP is degraded to hypoxanthine and because of further degradation with xanthine oxydaze (present in vascular endothelial cells) during reperfusion and reoxygenation, supraoxide O_2- is produced. This O_2- free radical can induce a further creation of new free radicals that can break down cell membranes. Normally, the cell creates enough free radical scavengers (FRS) to rid the cells of these toxins by further degradation. However, with ischemia, these are not sufficient and additional FRS may be required to prevent further injury. The crucial period appears to be 0-2 hours after revascularization. In the case of some pharmacological substances like Calcium channel blockers (verapamil, nifedipine, diltiazem), if administrated immediately before revascularization, it inhibits calcium-induced phospholipases, which can start a cascade reaction that amplifies the destructive effects of ischemia (7). Most transplant studies successful in decreasing postoperative acute tubular necrosis require loading of Calcium channel blockers just before revascularization as well as two days postoperatively (7,8). These postulates are successfully applied to renal transplantation and it seems logical for the same procedure to be applied with other surgical procedures which require hypothermia and revascularization as ANL.

According to the results presented, ANL seems to be a relatively safe one-stage procedure in the treatment of staghorn lithiasis. The total stone free rate is achieved in 83% of the cases, which is a referent result against literature (10). Only 17% of the total number of cases had residual stones less than 1 cm, which was successfully treated with ESWL. Intra and postoperative complications were marginal and did not influence operative procedure, and all complications were treated conservatively. Mean operative time was less than three hours, with mean CIT of only 61 minutes. Relevant studies allow cold ischemia time up to three hours (11). Additional safety factor was administration of verapamil in prevention of reperfusion injury. The patients follow up showes that global renal function is stabilized and even improved in patients with chronic renal failure, while an especially good outcome was observed in patients with preoperative normal serum creatinine values. Although recent reports show results of modified ANL (12), there is no significant difference between the standard and modified ANL with respect to its operative time and final outcome. Some of the studies report even better outcomes for the standard ANL in patients with chronic renal failure (13).

Considering the criteria for treatment of staghorn stones, established by American and European Urologic Association (1, 14), ANL should remain the procedure of choice in the case of severe damage of renal architecture (calyceal distortion, infundibular stenosis, hydronephrosis, ureteropelvic junction obstruction), as well as in patients with high BMI. In this study, 83% of the cases had calyceal distortion and infundibular stenosis, additionally complicated with PU obstruction in 55% of the cases,

implying that percutaneous and endoscopic procedures would be an inappropriate treatment choice. Further more ANL is a one-stage procedure with high stone free rate (15). According to some citations (16) there is a higher risk for successful ANL treatment in centers that are not exclusively specialized for intrarenal surgery. However, the results presented in this study prove that ANL can be safely done in less specialized centers.

Conclusion

The results of cases presented prove that ANL combined with recommended prevention of reperfusion injury still has its place in treatment of patients with staghorn calculi and damaged renal architecture. ANL ensures a high stone reduction rate and low level of complications in carefully selected cases.

References

(1) Preminger G., Assimos D., Lingeman J., Nakada S., Pearle M., Wolf, J. Jr. AUA Guideline on management of staghorn calculi: diagnosis and treatment recommendations. J. Urol. 2005: 173 (6): 1991-2000

(2) Lingeman J.E. Lifshitz D.A., Evan A.P. Surgical management of urinary lithiasis, In: Campbell's Urology, Volume 4. (eds. Walsh P.S., Retik A.B. et al). 8th edition, W.B. Saunders Company, Philadelphia, 2002, pp: 3361-3387

(3) Sharma R.N., Shah I., Gupta S., et al. Thermogravimetric analysis of urinary stones. Br. J. Urol. 1989; 64: 564–566

(4) Gettman M.T., Segura J.W. Struvite stones: Diagnosis and current treatment concepts. J. Endourol. 1999; 13:653–658

(5) Boyce W.H., Smith M.B.J. Anatrophic nephrotomy and plastic calyorraphy. Trans. Am. Assoc. Genitourin. Surg 1967; 59:18

(6) Novick A. Surgery of the kidney, In: Campbell's Urology, Volume 4. (eds. Walsh P.S., Retik A.B. et al). 8th edition, W.B. Saunders Company, Philadelphia, 2002, pp: 3570-3636

(7) Bretan P.N. Jr. Extracorporeal renal preservation, In: Stewart's operative urology-The kidneys, the adrenals and retroperitoneum, Volume 1., 2nd edition, Williams & Wilkins 1989, pp:301-311

(8) Shapiro R. The Transplant Procedure, In: Renal Transplantation, (eds. Shapiro R., Simmonds R.L., Starzl T.E.), Appleton Lange, Stamford, Connecticut, 1997, pp: 103-157

(9) Marberger M. Renal hypothermia in situ. In: Stewart's operative urology-The kidneys, the adrenals and retroperitoneum, Volume 1, 2nd edition, Williams & Wilkins 1989; pp: 51-59.

(10) Boyce W.H. The localization of intrarenal calculi during surgery. J. Urol. 1977; 118:152

(11) Griffith D.P., Gibson J.R., Clinton C.W. et al. Acetohydroxamic acid: Clinical studies of a urease inhibitor in patients with staghorn renal calculi. J. Urol. 1978; 119-124

(12) Ramakrishnan P.A., Al-Bulushi Y.H., Medhat M., Nair P., Mawali S.G., Sampige V.P. Modified anatrophic nephrolithotmy: A useful treatment option for complete complex staghorn calculi. Can. J. Urol. 2006;13(5):3261-3270

(13) Kijvikai K., Leenanupunth C., Sirisriro R., Lertsithichai P. Comparative study of renal function between standard and modified anatrophic nephrolithotomy by radionuclide renal scans. J. Med. Assoc. Thai. 2004; 87(6):704-708.

(14) Tiselius H.G., Ackermann D. et al. Guidelines on urolithiasis; Eur. Urol., 2006, 7: 31-33

(15) Assimos D.G. Anatrophic nephrolithotomy. Urology, 2001; 57(1):161-165

(16) Hinman F.J., Kidney excision. In: Atlas of Urologic Surgery, 2nd edition, WB Sounders Company Philadelphia, 1994., pp: 983-1056