Review Article

Etiopathogenesis and management of bladder dysfunction in patients with posterior urethral valves

Joseph Thomas

Department of Urology, Kasturba Medical College, Manipal, India

ABSTRACT

Posterior urethral valves are the commonest cause of urethral obstruction in a male child. It has significant effects on the development of upper urinary tracts and in the evolution of urinary bladder function. The effect on the kidneys and the urinary bladder persists even after the successful management of the obstructing valves. A detailed evaluation of the associated bladder dysfunction will help in planning management protocols that will improve the long-term outcome of these patients.

Key words: Bladder dysfunction, posterior urethral valve, valve bladder

INTRODUCTION

Posterior urethral valve (PUV) is the commonest cause of lower urinary tract obstruction in male infants with an estimated incidence of 1:25,000 live births and 1:5000 male infants.[1] The initial clinical presentation used to be delayed with the affected children presenting with obstructed voiding, recurrent urinary infections, and renal failure. Although the incidence of PUV has remained stable, the widespread use of prenatal ultrasound evaluation has significantly increased its early diagnosis and management. In fact, posterior urethral valves are now commonly diagnosed by the postnatal evaluation of infants who were diagnosed with prenatal hydronephrosis.[1] Initial catheter drainage and the eventual definitive management by valve ablation could alleviate the urethral obstruction rapidly. The associated metabolic derangements if any can be normalized without delay. These successful initial management protocols have lowered the early mortality to 3%. However, it is a matter of concern that even after the early successful treatment of valves, these children continue to have persistent problems with a long-term morbidity that often result in end-stage renal disease (ESRD). It has been found that the incidence of chronic renal failure (CRF) was 34% and ESRD was 10% at the end of 10 years, and the incidence increased to 51% having CRF and 38% having ESRD at 20 years.[1] The cause of the initial peak of ESRD in the first year of life is due to the inherent developmental renal dysplasia. A second peak seen in late childhood and adolescence is due to secondary renal damage. The unidentified bladder dysfunction which persists over a period of time is the most important cause of this late renal deterioration. While there is no control over the developmental renal dysplasia, a better understanding of the bladder behavior and its appropriate management could prevent the deleterious long-term problems in these children. There is now wide acceptance that maximizing the long-term outcome in PUV patients centers on maintaining bladder function.

For correspondence: Dr. Joseph Thomas, Department of Urology, Kasturba Medical College, Manipal 576 104, India.
E-mail: drjosephthomas@yahoo.co.in

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EFFECT OF POSTERIOR URETHRAL VALVES ON BLADDER DEVELOPMENT

During the normal bladder development, the fetal bladder fills with urine that is emptied cyclically from early in the intrauterine period. In the last trimester, the voiding frequency is approximately 30 times in 24 h. This normal bladder cycling generates stretch forces that result in a decrease in the total collagen content in the bladder wall that is associated with a reduction in the smooth muscle tension. Thus, a normal compliant bladder is produced. In patients with PUV, this normal bladder recycling fails

and the bladder function is altered. The nature of this bladder dysfunction depends on the severity of the urethral obstruction, and the timing during gestation at which this obstruction develops. The response of urinary bladder to partial outlet obstruction-like PUV progresses through three stages.[2]

Initial period

There is a rapid increase in the bladder mass and capacity. However, there is a temporary reduction in the bladder's ability to contract and generate pressure, after which the ability to sustain the pressures and empty is restored. Although there is near complete bladder emptying, the voiding pressures are higher.

Compensated phase

Although the bladder mass stabilizes, the pressure generation remains above the control levels. There is impairment in the bladder capacity and compliance due to changes in the smooth muscle and collagen distribution. This is demonstrated by an *in vitro* reduction in the contractile capacity of the smooth muscles. There is often partial bladder denervation that is present which is reversible on relief of the outlet obstruction. However, in the presence of continuing obstruction, the bladder destabilizes over a varying period of time to the final stage.

Decompensated stage

There is progressive increase in bladder capacity with decrease in the bladder compliance, contractility, and ability to empty.

The summative effect of all the bladder changes that occur in patients with PUV result in a valve bladder. These effects can be at different levels:

Changes on muscles and extracellular matrix

The injury to the lower urinary tract is basically caused by the response of bladder to continuing mechanical impediment that result in high-pressure urine storage and voiding.[3] The bladder is initially capable of generating higher voiding pressure and empties almost completely. There is hypertrophy of smooth muscles and increase in the deposition of extracellular matrix (ECM) in the blabber wall.[4] As the bladder smooth muscles increase the contraction effort, the structure and function of the bladder change. The abnormalities in the bladder outlet and sphincter areas also influence the smooth muscle function. The finely tuned neurosensory perception of pressure or stretch accompanying the higher voiding pressure is relayed through reflex arcs and increases the motor demand on the detrusor. It is interesting to note that the bladder smooth muscle retains its capacity for normal function despite the development of the obstruction *in utero*. This is proved by the apparent normalization of the bladder morphology and function after the valve fulguration. This contrasts with the smooth muscles in neurogenic bladders where the phenotypic changes are more permanent.[5]

Experimental models of fetal partial bladder outlet obstruction have given an insight into the pathophysiology of evolution of bladder changes. The common theme across all the models is the marked deposition of ECM between the muscle bundles.[4] Both structural and nonstructural components of the bladder have major effects on smooth muscle function through effects on matrix rigidity and signaling through ECM receptors. The prominent deposition of ECM alters both the active and passive properties of the bladder wall. Although the ratio of the muscle to connective tissue is the same as in normal bladders, there is conflicting evidence that the type of collagen within the bladder wall is altered. There is increase in the ratio of type III to type I collagen and the type III collagen infiltrates the detrusor muscle bundle. Studies with epithelial cells and smooth muscle have shown that ECM orchestrates the quiescent, migratory, or proliferative cellular behavior.[4] Structural ECM proteins, in concert with adhesive proteins, provide crucial structural support to the bladder. It is an interesting question if bladder has a functional reserve, which can be called to function without penalty.[6]

Cellular changes

The progressive stretch injury by outlet obstruction leads to a nonreversible process with changes in the cellular and extracellular characteristics of the bladder wall, leading to bladder dysfunction.[7] The over distension of the bladder alters the detrusor blood flow resulting in ischemia and decreased perfusion to the detrusor.[8,9] There is a shift to anerobic metabolism and the nerves within the bladder wall are damaged.[10] In a rabbit model of overactive bladder, it was found that there was free radical-mediated ultrastructural damage and neurodegeneration in the overactive bladder.[8,9] Over activity-associated mitochondrial stress may have a central role in epithelial damage, smooth muscle cell injury, and neurodegeneration. Superoxide dismutase and aldose reductase upregulation in the overactive bladder imply intrinsic defensive reaction against free radicals that apparently fails to prevent oxidative damage and neurodegeneration.[10] Therapeutic strategies targeting basic mitochondrial processes such as energy metabolism or free radical generation may help better manage wall degeneration and neuropathy in the overactive bladder.[11,12] A proper understanding of the molecular pathways that damage the bladder wall-following outlet obstruction will help to develop pharmacologic intervention to avoid bladder injury. In neonatal dogs with urethral obstruction, the use of angiotensin converting enzyme inhibitor captopril decreased the collagen content of the lamina propria and muscular layer in the ureter.[13]

Glycogen as a marker

The glycogen content of the detrusor muscle from a guinea

pig model was studied to determine if the detrusor glycogen content after removal of urethral obstruction reflects the nature of bladder dysfunction.[14] The degree of glycogen deposition in a bladder after the removal of obstruction correlated directly with bladder function during obstruction. The highest glycogen deposition was found in bladders that experienced the highest pressures, most instabilities, lowest compliance, and highest contractility. Thus, high glycogen content reflects a history of abnormal urodynamic function and exemplifies the added value of structural analysis to urodynamic studies.[15] The glycogen content of a bladder also reflects the past history of bladder dysfunction, during recovery period. This window on the functional history of a bladder may be of clinical value for picking out potential bad-responders to therapy especially with incomplete data on bladder function during a previous period of bladder obstruction.[15]

Clinical effects

As this filling and emptying cycle repeat in the presence of continuing outlet obstruction, there is further remodeling of bladder wall. Although the bladder continues to produce higher pressures, they are inefficient and the postvoid residual urine increases. The increased urinary output in the fetus also puts additional stress in this obstructed decompensating system. The detrusor decompensates as the bladder cannot keep pace with the functional demands. The bladder gets overstretched by the excessive bladder storage for a longer duration. This is the dominant insult that erodes bladder function. The high bladder neck that is often seen in the PUV patients was once mistaken as a cause of obstruction and was surgically incised to facilitate bladder emptying. It is now understood that this appearance of the bladder neck is due to the hypertrophy because of the distal obstruction and is not an obstructive lesion by it. Bladder neck appearance and function usually improve after the obstructive valves are ablated.

EFFECTS OF POSTERIOR URETHRAL VALVES ON RENAL AND BLADDER FUNCTION

Urinary bladder takes the brunt of damage in PUV and most of the children suffer significant bladder dysfunction lifelong. The important aspects of these damaging effects are:

Clinical patterns

There are three main clinical patterns of urinary bladder in patients with PUV.[16] They are: (1) hypertonic low compliant, small capacity bladder, (2) hyperreflexic bladder with uninhibited contractions, and (3) myogenic failure with valsalva voiding and overflow. A group of conditions was identified in patients with posterior urethral valves with persistent upper tract dilatation following valve ablation. This included a noncompliant thick-walled bladder, urinary incontinence, and nephrogenic diabetes insipidus. Subsequently, the pseudonym "valve bladder syndrome" became associated with this phenomenon.[17] It is also proposed that valve bladder syndrome is not a permanent state due to prenatal bladder damage, but is an induced condition due to a combination of polyuria, impaired bladder sensation, and residual urine volume.[18]

The bladder dysfunction shows a changing pattern that is related to the age of the child.[19] Infants at 0–1 year has reduced functional bladder capacity that is associated with detrusor over activity. During 1–3 years though the bladder capacity increases, over activity persists, and bladder emptying is incomplete. At 4–12 years, there is a further increase in capacity with the absence of overactivity during filling, decreased contractility during voiding and increase in residual volume. Thus, the condition of valve bladder is one that is in constant transition during childhood. It is important to know if these bladder changes are reversible after valve fulguration and thus arrest the progression of bladder dysfunction. The valve patients who have been followed for many years with urodynamic studies have shown a clinically apparent evolution in urodynamic anomalies, which change over time with age.[19,20] The urodynamic pattern of hyper contractility generally found soon after valve ablation gradually changes to hypocontractility, and this pattern seems to be the rule after puberty. However this change with time is unpredictable, which emphasizes the need for constant follow-up even in patients who do not have symptoms.[21] When the original abnormality is minor, the changes reverse after valve fulguration with functional improvement. However, children with initial significant bladder dysfunction will seldom grow out of it, and as the anomalies worsen, it may precipitate renal failure.

Urodynamic changes

It has been suggested that proactive urodynamic directed bladder management might improve long-term bladder outcome after valve fulguration. Urodynamic studies are necessary to track changes and to alter management in these patients throughout the first two decades of life.[17] Is it possible to reduce the incidence of the terminal myogenic failure by proactive, early aggressive use of urodynamic studies to identify and appropriately manage the secondary effects of valve disease? There is thinking that myogenic failure is more likely to be secondary to anticholinergic therapy than a preordained consequence of valve disease.[22] However, this is more of an observation than a properly conducted controlled study. Video-cystoscopy in those PUV patients with myogenic failure showed the posterior bladder neck lip to be elevated, which was strongly suggestive of hypertrophy.[23] This observation suggested that myogenic bladder decompensation secondary to bladder neck obstruction coexisted in many PUV patients. However, it cannot be deducted from the above study that bladder neck hypertrophy had produced myogenic failure.

Upper tract function

Continuing damage to the already deranged upper urinary tract function is an important long-term problem in valve patients. This makes long-term assessment and follow-up of upper tract functions after valve ablation an important aspect of postfulguration follow-up.[24] In the follow-up of children after valve fulguration, nadir serum creatinine and bladder dysfunction were the two main prognostic factors correlating with long-term renal outcome.[25,26] Although the effects on the upper tracts remain throughout the growth period, there are two points in life when this damaging effect is maximally detrimental—one in the newborn period and the second one late in childhood. The proper drainage of the upper urinary tract is hampered by a combination of poor bladder sensation, high bladder volumes, and poor compliance producing high storage pressures. Both the hyper contractile bladder of infancy and the rigid bladder of late childhood inhibit upper tract drainage and worsen renal function.

Evaluation of persistent hydronephrosis in valve patients is complex as it is produced by a combination of renal and bladder abnormalities. It requires measurement of voided urine volumes and postvoid residual urine to evaluate the relationship between renal tubular competence and bladder function. There is a direct correlation of abnormal urodynamics, indicating poor compliance and detrusor over activity with poor renal functional outcome.[27] Excessive bladder filling even at normal pressures also have a detrimental effect on renal function when the renal units are chronically dilated.[28] Synchronous cystometry and dynamic renograph can demonstrate the critical volume of filling that prevents upper tract drainage and helps in planning management. In patients with bladder volume-dependent upper tract obstruction, bladder function can be stabilized by consistently maintaining bladder volume below this critical level. Most of the children with persistent hydronephrosis do not need surgical therapy other than valve ablation and attention to bladder function.

Voiding problems

At least one-fourth of patients with PUV continue to experience long-term voiding problems even after successful valve fulguration.[17] It is increasingly been recognized that bladder is an important participant in the chain of events, with bladder dysfunction being the predominant cause of the persistent problems after valve fulguration. Poor urinary stream and incontinence are the two main complaints. The other complaints include urinary frequency, recurrent urinary tract infection, and renal failure. In the past, the poor urinary stream was falsely attributed to the hypertrophied bladder neck and many open and endoscopic procedures were done on the bladder neck to improve the urinary stream.

Incontinence is the hallmark of bladder dysfunction in patients who have undergone successful fulguration of the PUV. The entire focus was on a wide-open dilated posterior urethra as the cause of incontinence. The patients were asked to wait till puberty with the assumption that the development of the prostate would improve continence. Incontinence was also thought to be due to sphincter injuries during valve fulguration and the bladder neck dysfunction. However, incontinence is now understood as a clinical indicator of an underlying bladder dysfunction that has to evaluated and corrected. The cause of incontinence is now understood to be multifactorial due to a combination of poor bladder sensation, poor bladder compliance, detrusor instability, and polyuria. Varying studies have shown delayed day and nighttime continence[29,30] with only 53% dry by the age of 12 years.[30] This problem may improve in most of the patients by 20 years of age. However, the delay in attaining continence causes painful difficulties to the patients and their families during adolescence .[31] Although all the men with a past history of PUV were continent, there were signs of bladder dysfunction in 40% and all these subjects had bladder symptoms, suggesting detrusor weakness as the cause.[32] It is important to recognize that management of bladder dysfunction is the only possible factor amenable to correction to avoid development of renal failure.[33] The importance of bladder dysfunction in patients with PUV suggests the possible role of screening as urodynamic evaluation yields a higher incidence of abnormal bladder especially when there are clinical symptoms.[34] However, it is equally important to understand that normal urodynamic findings in the PUV patients do not preclude renal deterioration.[28] The renal tubular damage, which progresses during childhood, leads to inability to conserve sodium and free water and can lead to nephrogenic diabetes mellitus with production of large urine volumes. These exaggerated urine volumes can overcome the functional ability of the bladder and more so in one with limited functional potential.

FACTORS AFFECTING LONG-TERM OUTCOME

There have been many interesting observations that could be made out of the various management protocols that have been followed in PUV patients in the last five decades. These are helpful in evaluating the management aspects in PUV patients, especially to have a long-term favorable outcome in mind. The important observations are:

Antenatal intervention

Posterior urethral valves are now increasingly being diagnosed during the routine antenatal ultrasound evaluation. Is there a role for vesicoamniotic shunting in maintaining normal bladder function and prevent bladder dysfunction? The multicenter PLUTO trial, which is looking in a randomized controlled manner into the benefits of antenatal shunting, is hoped to throw more light into the beneficial outcome of this antenatal intervention.[35]

Neonatal fulguration

PUV is now commonly diagnosed during the postnatal period and the obstruction is relieved early. What is the effect of this early relief of obstruction on the evolution of bladder dysfunction? It was found that neonatal valve ablation would protect the bladder functions and allow normal bladder cycling and healing. This underscores the importance of routine prenatal screening and early intervention for the valves.[36] What is the functional outcome on renal and bladder function in the second decade when the valves prenatally detected and treated in the neonatal period? The functional outcome of patients aged 10–23 years who had undergone neonatal fulguration was considerably better than those who clinically presented late. These findings suggest that the long-term prognosis of PUV might be improved by prenatal diagnosis.[37]

Late presentation

Is the bladder function different in those who present later in childhood?[38] There was a significantly lower rate of detrusor over activity (15%) in those patients with late presenting PUVs. The urodynamic parameters between the early and late presenting groups did not reveal any significant difference. In a study of 70 children who presented at the average age of 7.5 years, it was found that ablation of valves will dramatically improve symptoms of urinary frequency and diurnal and nocturnal enuresis. Despite this improvement, enuresis, urinary frequency and poor bladder emptying persisted requiring further treatment.[39] The continuing bladder dysfunction suggested that irreversible urinary tract damage might have already occurred even at the time of valve fulguration.

PUV with renal failure

Patients with PUV used to present late with renal failure and infections which necessitated a temporary urinary diversion by uretrostomy or vesicostomy.[40] The nonavailability of pediatric instruments for neonatal fulguration was also another indication for a temporary urinary diversion.[41] Does this urinary diversion affect the final functional bladder outcome? A vesicostomy was believed to have a detrimental effect in those boys with posterior urethral valves compared to those who had undergone primary valve ablation.[42] It has been found that primary valve ablation is associated with better bladder functional outcome than vesicostomy and should be the initial treatment of choice in PUV.[43,44] However, when the diversion procedures are required it can be done safely as a temporary measure without worsening the bladder dysfunction.

ROLE OF URODYNAMIC STUDIES

A proportion of boys with PUV will have normal bladder function. However, there is no way in which this can be predicted early in life. Bladder function is abnormal in up to 70% of older children and adolescents despite treatment with fulguration of the obstructing valves which has been implicated in the late deterioration of renal function. A poor understanding and inappropriate management of bladder dysfunction can result in unnecessary morbidity, which can handicap a child for life. Urodynamics provides a useful tool to test the efficacy of treatment as well as determine any refinements that is necessary to improve the outcome of such treatment.[45,46] The objective of urodynamic assessments in children is to reproduce the patient's complaints or symptoms. Broadly, the investigations can be classified into noninvasive urodynamics and invasive urodynamics.

Noninvasive methods

The noninvasive methods can be performed in all children to select the patients who require a detailed invasive evaluation. A good medical history will help in understanding the voiding problem being assessed. It is also important to assess the home and school environment of the child. This will influence the management options that are being considered to make it practical and compliant in the normal home and school environment. Frequency/volume diary gives useful information about the voiding problem in the home environment. The diary also gives an idea about the functional bladder capacity at daytime and the volume voided in the morning after a dry night, which reflects the maximum bladder capacity. The voiding diary is also a simple method to assess the efficacy of treatment with medications. Two free voids into an uroflowmeter observing the child's posture and efforts at abdominal straining gives the flow pattern and the voiding efficiency.

The invasive studies

These categories of invasive studies include natural filling urodynamics, standard cystometrogram, and video contrast filling cystogram or isotope filling cystogram. Video urodynamics can provide additional information that may contribute to a further understanding of the problem under investigation. Ensuring the cooperation of the child is of utmost importance to obtain reliable and reproducible results. The indications for invasive urodynamic studies include (a) persistence of day time incontinence beyond 5 years of age, (b) increasing upper tract dilatation, (c) deterioration of renal function, (d) to assess the efficacy of medical treatment, and (e) prior to renal transplant to optimize the results. It is prudent to wait for at least 6–12 months after valve fulguration to allow for the compensatory changes in the bladder to settle before invasive urodynamic studies are carried out. The catheters are ideally placed 24 h before the study under anesthesia. This makes the study less traumatic for the child and ensures the cooperation of the child for a meaningful study. The natural filling urodynamics is known as Physiological Fill Urodynamic Study. The advantage of physiological process, which can be done on an ambulatory and overnight process that avoids over activity, is offset by the longer time it takes to complete the study. The Artificial Fill Urodynamics can be done faster, and

fluoroscopy can be used for better information. However, the temperature of the fluid and the rate of filling can affect the results due to the induced detrusor over activity. The urodynamic studies can be misleading if the actual bladder pressures and the volume are not taken into consideration. A bladder with a large volume may be interpreted as having good compliance. However, it may still have high end filling pressures that could be detrimental to the upper tracts. This would be magnified in a patient with ineffective bladder emptying. The studies may have to be repeated depending on the response of the child to the various management strategies. The possibility of the changing bladder dynamics over time also makes it necessary to repeat the urodynamic studies.

PRINCIPLES OF BLADDER MANAGEMENT

The management principles in PUV patients aim at urine storage and emptying without elevation of the bladder pressures to a level that is detrimental to upper urinary tract drainage. A proper understanding of the underlying bladder pathology is important for the proper planning of the management of the bladder dysfunction. This includes a proper voiding diary supplemented by appropriate structural evaluation and urodynamic studies? The following are the various management aspects, which have to be appropriately combined in a given patient according to the underlying problems.

Behavioral modifications and timed voiding

All the patients have to be first started on a behavioral protocol. This includes educating the children and the parents about the bladder functioning, need for adequate fluid intake, recognizing the urge sensation, need for regular bladder emptying and eradication of urine holding maneuvers. Patients should be taught about timed voiding, double voiding, and effective catheterization as needed. It is also important to suggest ways to solve constipation, which is often present in these patients.

It is possible to achieve adequate bladder emptying by a simple method of timed voiding. This should involve voiding not only during the waking time, but also during the sleeping time. However, it may be difficult to achieve this in a child who has not got voluntary control over micturition and may not follow the instructions of the parents for bladder emptying. If it is not possible to achieve complete emptying of the bladder by various voiding methods, then clean intermittent catheterization (CIC) can be added to keep the bladder empty. The frequency of CIC depends on the severity of bladder dysfunction.

Nocturnal bladder management

This involves timed emptying of the bladder or continuous drainage as an adjunct to the treatment of bladder dysfunction. This treatment is derived from the hypothesis that valve-bladder syndrome is associated with a persistent bladder dysfunction characterized by chronic over distention of the urinary bladder, which is exacerbated by associated polyuria.[47,48] The daytime emptying can be ensured by timed voiding. However, there is a long period of time when the child sleeps when the bladder will remain full through out the night. The pressures generated will impair the upper tract drainage with further deterioration of renal function. Nocturnal bladder drainage is a simple and safe therapeutic maneuver for this pathophysiological situation, which will reduce the frequency of UTIs, improves upper tract dilatation and improves continence. Overnight drainage in conjunction with daytime CIC can be an appropriate management in children with poorly compliant bladders, especially in the early stages of renal compromise.[47,48]

Biofeed back and pelvic floor exercises

Children with urodynamically proved lower urinary tract dysfunction after successful valve ablation could be managed by biofeedback therapy and home pelvic floor exercises.[49] Biofeedback therapy and home pelvic floor exercises could provide significant and durable relief for persistent lower urinary tract dysfunction after valve fulguration. There was an overall consistent good response in 70% of the patients. This could possibly avoid or reduce anticholinergic drugs and avoid CIC. Alpha-blockers can be used if the simple method of timed voiding is not able to achieve the expected benefit of keeping the bladder empty.[50] It was found that the use of Terazosin (0.25–2 mg) after the PUV fulguration improved bladder emptying with significant reduction in the postvoid residual urine. Hypotension was not a significant side effect of α-blockers in these children.[51]

Drug treatment

A variety of agents have been used to treat bladder over activity. Many of the drugs are no longer used in clinical practice (and this includes the most commonly tested—flavoxate). There is inadequate evidence to determine whether any of these drugs are better or worse than anticholinergic medications.[52] Anticholinergic agents are commonly used to treat reduced bladder compliance and the over activity during bladder filling. During the initial treatment period, there was more symptomatic improvement when anticholinergics were combined with bladder training as against each modality alone.[53] Agents such as imipramine, oxybutynin chloride, and tolterodine tartrate have been found to be effective for overactive bladder. Although there are other medical alternatives such as darifenacin, trospium chloride, and solifenacin succinate is available, their safety in children is not known. The safe dose in children is Oxybutynin 0.2 mg/kg BID to QID, Probanthine 0.5 mg/kg BID to QID, and Imipramine 0.7–1.2 mg/kg BID to QID. The review of the results of anticholinergic medications in adults has shown that there is significant improvement in the urinary symptoms.[54] Imipramine (1.5–2 mg/kg) is an effective and cheap drug for valve bladders. It has shown

significant symptomatic improvement in patients with noncompliant or unstable bladders after PUV fulguration both clinically and with urodynamic studies.[55] Dryness of mouth was the commonest side effect of the anticholinergic medication. However, this side effect did not have any effect on the number of withdrawals from anticholinergic treatment. It is not clear if the benefits are sustained during long-term anticholinergic treatment or after stopping the treatment.

Oxybutynin inhibits stretch-induced bladder smooth muscle cell proliferation *in vitro* studies.[56] *In vivo* studies in animals treated with oxybutynin showed that they retained the normal intravesical pressure, detrusor over activity, and compliance. The oxybutynin group showed less collagen infiltration in the detrusor with fewer glycogen granules. These results demonstrate the protective effect of oxybutynin on bladder function and structure. This effect on the hypertrophic and ischemic bladder changes is an argument for an early start of oxybutynin treatment in children with urethral valves.[56]

Oral tolterodine is preferred over oxybutynin because of the reduced risk of dry mouth. Extended release preparations of oxybutynin or tolterodine are preferred to immediate release preparations because there is less risk of dry mouth.[57] There were insufficient data from trials of other anticholinergic drugs to draw any conclusions. The use of anticholinergic agents may not be optimal due to the ineffectiveness of the drug or due to the side effect of the agent used. It was found that the use of two anticholinergic medications simultaneously (10–30 mg oxybutynin, 4 mg tolterodine, and/or 5–10 mg solifenacin) could optimize the medical therapy for children in whom single agent anticholinergic therapy has failed.[58] The use of adjunctive intravesical oxybutynin therapy increased the mean maximum bladder capacity and decreased bladder pressure in children with neurogenic bladder. However, the level of evidence available is insufficient to recommend this therapy.[59] Inappropriate use of anticholinergic medications may induce iatrogenic myogenic failure. Therefore, they should be used only with urodynamic monitoring.[23] This drug-induced myogenic failure is reversible on stopping treatment.[22]

Clean intermittent catheterization

It may not be possible to keep the bladder empty by the simple methods of timed voiding and double voiding because of the inherent ineffective detrusor contractions or as a side effect of the anticholinergic medications. This necessitates the use of catheters to empty the bladder. CIC could be initiated at an early age when it is indicated. There were no serious complications of CIC, and there was a significant improvement in bladder instability and bladder. Moreover, the renal function also improved with an increase in the median differential glomerular filtration rate.[60] It was interesting to note that in this study there was functional renal deterioration in those patients who stopped CIC. The sensate perineum and the dilated posterior urethra may make doing CIC difficult in a child leading to noncompliance and deterioration of upper tracts. An abdominal catheterizing channel may be a viable alternative to keep the bladder empty.[61]

Bladder neck management

Historically, secondary bladder neck obstruction has been over diagnosed in patients with PUV and was thought to be an important cause of persisting voiding abnormality after valve fulguration. Endoscopic bladder neck incision or open bladder neck repairs used to be made with poor clinical outcome. The effects of simultaneous bladder neck incision and valve ablation on urodynamic abnormalities were studied in patients with posterior urethral valves. At mean follow-up of 4.5 years, it was found that the detrusor over activity was more in the patients who did not have bladder neck incisions.[62] The need for anticholinergic medications was also more in the patients who did not have bladder neck incision. Thus, valve ablation with bladder neck incision may result in better bladder urodynamic function in comparison to simple valve ablation.[62] However, this is a selective subgroup of patients and long-term studies with follow-up through puberty are required to evaluate to identify the role of bladder neck ablation in PUV patients.

Bladder augmentation

Augmentation of the bladder may be required in PUV patients with valve bladder when medical management fails to prevent the deterioration of renal function. Bladder augmentation significantly improves the health-related quality of life in children and young adolescents with valve bladders.[63,64] This can be an enterocystoplasty or colocystoplasty using a segment of ileum or colon. The metabolic consequences and long-term complications associated with incorporating intestines into the urinary system have to be thought of in the pediatric patient before considering augmenting the bladder with intestines. A better awareness and understanding of these complications will lead to improved prevention, surveillance, and treatment of the complications.[65,66] Although bladder augmentation with ileum or colon has been shown to be safe, the long-term effects of metabolic acidosis in addition to abnormalities in linear growth and bone metabolism remain largely unknown. In the short-term, children after augmentation will have varying degrees of metabolic acidosis which, overtime, appears to resolve with no affect on linear growth.[67] In the long-term follow-up of pediatric augmentations, there is a very minimal, but definite incidence of malignancy in the augmented bladder.[68] Ureterocystoplasty is another option for augmenting the bladder especially in boys with impaired renal function.[69] There have been concerns regarding the efficacy of ureterocystoplasty as a form of bladder augmentation. It has been found that enterocystoplasty achieves a better storage function outcome.[70] However,

there is durable functional and urodynamic improvement with ureterocystoplasty in valve bladder patients.[71]

Renal transplantation

Renal transplantation may be required in the management of PUV patients, an up to 50% can end in ESRD.[72] There are concerns about poor outcome with an increased risk of graft dysfunction and urinary tract infections. However, the results of graft function were similar to that obtained in the general transplant population.[73,74] There was a greater incidence of urological complications in those who had PUV. Preoperative bladder management and continued monitoring of bladder and kidney function postoperatively are of paramount importance in the preservation of allograft function. This may require the need for improving the bladder capacity with augmentation. Augmentation cystoplasty is a safe and effective option to treat patients with ESRD undergoing kidney transplantation. However, there is a potentially high risk of surgical complications in the long-term follow-up of these patients.[75,76] Reconstruction of the lower urinary tract followed by renal transplantation is a safe and efficient approach. It has the advantage of restoring the lower urinary tract before immunosuppressive therapy, and supplies the best possible reservoir for a transplanted kidney. However, it has been found that there was no significant difference between the augmented and nonaugmented group as regards the renal function or bladder capacity. Renal transplantation can be performed safely without preemptive bladder augmentation. The decision about the need for bladder augmentation should be made only after normal diuresis is restored.[77]

SUMMARY

The management of children with PUV is a continuous process that starts with the antenatal detection and early fulguration of the valves. The identification of the bladder dysfunction and its appropriate management will prevent the deleterious effects on the upper tracts and improves the long-term survival. Urodynamic studies will help in the identification of the type of bladder dysfunction that was initially present and helps in the planning of appropriate management. It also helps in the follow-up to recognize the changing pattern and plan changes in the treatment protocol. A judicious mix of behavioral management with medications and bladder drainage is important in all the patients. Bladder augmentation and renal transplantation are reserved for a select group of patients.

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