The Role of Alpha Blockers in the Treatment of Children with Voiding Dysfunction

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ABSTRACT:

BACKGROUND:

Voiding dysfunction is an important problem in childhood due to its relatively high prevalence and the fact that it may cause upper urinary tract deterioration with renal scarring. Pharmacological therapy is considered as one of the important measures to improve bladder emptying ,Several reports have supported the effectiveness of α-blockers in treating voiding dysfunction in children.

OBJECTIVE:

To evaluate the safety and efficacy of using selective alpha blocker therapy for children with voiding dysfunction.

PATIENTS AND METHODS:

A prospective study conducted from January 2011 to December 2013 in Al- Ramadi teaching hospital. 24 children with mean age 9.9 years had voiding dysfunction. Patients were evaluated by history, clinical examination, laboratory investigations, radiological examination, cystoscopy and urodynamic study. Treatment was initiated with doxazocin (selective α-adrenergic blocker) 0.03 mg/kg body weight and increased according to the response, but not more than 2mg, patients were followed monthly for 12 months.

RESULTS:

24 children (16 patient male and 8 female), all patients had high postvoiding residual volume and abnormally low maximum flow rate. 18 patients (75%) had vesicoureteral reflux and hydronephrosis, after the starting of doxazocin 20 patients (83%) showing improvement in their symptoms. Upper tract dilatation improved in 12 patients (66%), Mean postvoiding residual volume reduced by 72.7% of the pretreatment mean PVR (p = 0.0001),The increment in the maximum flow rate was 68.4% (p 0.0001) from the pretreatment maximum flow rate. Failure rate was reported in 4 patients(16%) subjectively and 6 patient (25%) objectively. No patients was reported to had any serious side effects to doxazocin.

CONCLUSION:

Selective α-blocker therapy seems to be well tolerated in children and appears effective for improving symptoms and bladder emptying in various pediatric voiding disorders.

KEY WORDS: voiding dysfunction, postvoiding residual volume, α- receptors doxazosin.

INTRODUCTION:

Dysfunctional voiding (DV) is a condition that describes an abnormal voiding pattern because of a lack of coordination between the detrusor and external sphincter during voiding after the normal age of daytime toilet training.[1]The current International Children's Continence Society (ICCS) terminology guidelines define a child with Dysfunctional voiding as one who habitually contracts the urethral sphincter during voiding.[2] The wall of the urinary bladder dome is composed of detrusor smooth muscle overlain by a mucosal layer on the luminal side and a serous coat of visceral peritoneum covering the roof and lateral walls. [3] The lower urinary tract is innervated by three sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems. The bladder outlet structures contain alpha adrenergic receptors therefore blocking these receptors can decrease the resistance of these outlet structure during resting and voiding .[4]

voiding dysfunction is a common clinical entity and is responsible for a maximum of 40% of pediatric urology visits.[5] Voiding dysfunction in children may be neuropathic or non neuropathic. Important neurological conditions include open and closed spina bifida(commonest group), sacral agencies, cerebral palsy, spinal cord tumors and trauma. Non neuropathic causes include, non neuropathicneuropathic(Hinmanin

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syndrome),Infrequent voiding syndrome, and frequency urge syndrome (unstable bladder).[6,7,8] Tools used to identify dysfunctional voiding include a detailed elimination history, bladder diary, urine flow measurement with uroflowmetry, and evaluation of postvoid residual urine (PVR) using an ultrasound and urodynamic study(UDS).[9]

The management armamentarium of DV in children includes several treatment modalities that involve a combination of cognitive, behavioral, physical, and pharmacologic therapies.[10] The regulation of micturition requires connections between many areas in the brain and extensive tracts in the spinal cord that involve sympathetic, parasympathetic and somatic systems. .[11] pharmacologic measures have focused on promoting bladder emptying by targeting the bladder outlet using alpha-adrenergic antagonists (alpha blockers). Alpha-adrenergic receptors have been demonstrated in the lower urinary tract (LUT), with a large concentration located at the bladder neck and throughout the human urethra.[12] Stimulation of these alpha-adrenergic receptors results in smooth muscle contraction and increased outlet resistance, whereas alpha-adrenergic blockade results in smooth
muscle relaxation and decreased bladder outlet resistance. Limitations of early
alpha blockers included their side-effect profile with hypotension and dizziness.

With later development of "selective" alpha blockers in the 1980s that targets α-1 rather than both α-1 and α-2 adrenergic receptors, these side effects were largely reduced.[13-16]

PATIENTS AND METHODS:

Twenty four children 5 to 15 years old (mean age 9.9) with voiding dysfunction who had lower urinary tract symptoms (LUTS) of more than 3months duration were enrolled in a prospective study including neuropathic bladder in 12 patients like meningomyelocele 6 patients , spinal cord injury 4 patients and cerebral palsy in 2 patients, and non neuropathic like, infrequent voiding syndrome in 4patients, the Hinman's syndrome in 2patients and underactive bladder syndrome (Lazy Bladder) in 6 patients. Those patients were treated with α-1adrenergic receptor antagonist, doxazocin, (cardura®,*pfizer*)0.03mg/kg body weight, at
department of urology in Al-Ramadi Teaching Hospital during the period January 2011 through December2013. Patients with anatomical abnormalities (urethral stricture, posterior urethral valves and bladder neck obstruction), on clean intermittent catheterization, history of augmented bladder surgery, and whom had vesicoureteral reflux more than grade three were excluded from the study.

Verbal ethical approval was taken from the family of the patients included in this study, the purpose, method, and side effects was explained to them. Patients age, sex and addresses were noted. History was taken from the family as well as the child if he was old enough to explain the symptoms, with a particular voiding history like; infrequent voiding(about one time per day), urinary retention, frequency (more than six times per day), dribbling, incontinence, painful urination, and recurrent urinary tract infection. Physical examination, focusing on the neurological examination, for all patients was done. Laboratory investigations were include complete blood count, blood urea, serum creatinine, urinalysis and urine culture and sensitivity. As a part of radiological examinations; abdominal ultrasound was performed to assess hydronephrosis and measure the post-void residual urine volume (PVR), in addition, voiding cystourethrogram was used to evaluate vesicoureteral reflux. Moreover uroflowmetry was done to measure the urine flow rate. Urethro-cystoscopy was performed under general anesthesia using 8FR pediatric cystoscope (*storz*)to exclude anatomical abnormalities like, urethral stricture, posterior urethral valves and bladder neck obstruction. Urodynamic evaluation of bladder capacity, filling and voiding pressure , presence or absence of abnormal detrusor contractions urethral pressure profile, and maximum urethral closure pressure .

Doxazocin a selective α- adrenergic antagonist, was administered to the patients
starting with a single daily dose of 0.5mg at bedtime, dose was gradually increased to a maximum of 2 mg/ day. Patients followed for 12 months for response assessment , Patients were followed within two weeks by symptomatic history, blood urea, serum creatinine, urinalysis, measurement of flow rate and ultrasound assessment of PVR and hydronephrosis, at this stage if the patient was satisfactory then treatment continued on the same dose, otherwise the dose
increased gradually. After that patients were followed monthly. During the period of follow up, if the degree of the hydronephrosis increased ,voiding cystourethrogram was advised to monitor the degree of vesicoureteral reflux, urodynamic evaluation was done only in the primary evaluation of the patients because it was unpractical to do Urodynamic evaluation in every follow up visits,

because it was not available in our city and the patients couldn't access it easily

The response to doxazocine was assessed clinically, by uroflowmetry and by ultrasound measurement of PVR. The duration of therapy lasting for12 months. The family awareness to occurrence of the possible side effects of medication (postural hypotension, dizziness, and headache) and their evident incidence was reported every visit. Parents were encouraged to give the medication before bedtime to minimize the potential of daytime postural hypotension.

Patients who was on antimuscarinics drugs should stop the drug before starting the study. One patient with meningocele had history of constipation and had been treated before the start our study. We start the study with 35 patients, but 11 of them did not continue the study because of various causes, being noncompliant, and missed during the follow up. So we proceed the study with evaluation of only 24 patients.

RESULTS:

During the period of study (January 2011- to December 2013), 24 children 16 of them were male and 8 were female with voiding dysfunction including neuropathic

in12 patients (50%) , meningomyelocele in 6 patients (25%), spinal cord injury in 4 patients (16.6%) and cerebral palsy in 2 patients (8.3%) , and non neuropathic like, infrequent voiding syndrome in 4 (16.6%), the Hinman's syndrome in 2(8.3%) and underactive bladder syndrome (Lazy Bladder) in 6 (25%) (table 1).

The youngest child was 5 years and the oldest one was 15 years old with a mean age of 9.9 years were treated with α-1 adrenergic receptor antagonist, doxazocin, with dose ranged from 0.5 mg to 2 mg once daily. The main symptoms were loin pain in 2 (8.3%), incontinence in 4 patients (16.6%), recurrent febrile attacks in 4 (16.6%), weak stream in 4 (16.6%), and retention in 10 (41.6%). These symptoms were improved in 20 patients(83%). Vesicoureteral reflux and hydronephrosis were noted in 18patients (75%) ,10 patients neuropathic (55,5%) and 8 non neuropathic (44.5%). Upper tract dilatation improved aftertreatment with doxazocin in 12 patients (66%), 6 neuropathic (60%) and 6 non neuropathic (75%). the most common finding in urodynamic study for the neuropathic type was detrusor hyperreflexia, striated sphincter dyssynergia, and smooth sphincter dyssynergia while the finding in the non neuropathic type ranged from finding similar to that of neuropathic type, to bladder capacity higher than expected for age and the compliance during filling is high , During voiding there is no detrusor contraction and voiding most often occurs with straining as in those with lazy bladder.

All the patients had large pretreatment PVR (greater than 10% of expected bladder capacity for age "in milliliters"),[17] the mean was 100.3 ml (Std. Error Mean ± 13.53), after starting doxazocin the mean PVR was 27.3 ml(SEM ±12.90). This is a reduction of average residual urine to (7.6%) of age expected capacity representing a (72.7%) reduction in the pretreatment postvoid residual urine (p = 0.0001). twelve patients (50%) were neuropathic dysfunction the mean pretreatment PVR 108.5 ml(SEM ±22.53) and the mean post treatment PVR 30.8 ml(SEM ±18.90), the reduction of mean PVR to age expected capacity (8.9%) and the reduction in the pretreatment PVR 71.6% (p =0.001).The rest 12 patients (50%) were non neuropathic had average pretreatment PVR 92.1(SEM ± 16.46) ml and mean post treatment PVR 23.8 ml(SEM ±19.26) which representing a reduction in mean PVR to (6.3%) of age expected capacity and a reduction in the pretreatment PVR 74.1% (p = 0.005) (table 2) .

Maximum urine flow(Qmax) was measured before and after treatment (normal Qmax> 15ml/sec)[55] overall mean Qmax were 6.65 ml/sec (Std. Error Mean ± 0.96) before and 21.1 ml/sec (SEM ±2.34) after treatment, (increased 68.4%, p0.0001). In neuropathic patients the mean Qmax 7 ml/sec (SEM ±1.10) before treatment and 18.5 ml/sec (SEM ±4.12)after (increased 62.1%, p=0.004), in non neuropathic mean Qmax was 6.25 ml/sec (SEM ±1.66), 23.8 ml/sec(SEM ±2.07)

before and after treatment respectively(increased 73.7%, p = 0.017) (table 3)

.There were 6 patients (25%) show no significant change in post-void residual after initiating therapy and slightly or no change in mean maximum flow rate of urine, 4 patients (16.6%) were neuropathic and 2 (8.3%) non neuropathic. From those 6 patient who failed objectively 4 patient (17%) show no improvement in their symptoms. During the period of study there was no significant side effect reported.

Table 1: Types of voiding dysfunction.

Types	No. of patients	%
Neuropathic bladder	12	50 %
Infrequent voiding syndrome	4	16.6 %
Hinman's syndrome	2	8.3 %
Under active bladder syndrome	6	25 %

Table 2: Response of post voiding residual volume of urine.

Types	Pretreatment Mean PVR(±Std. Error Mean)	Post- treatment Mean PVR(±Std. Error Mean)	reduction in PVR %	P value
Neuropathic bladder	108.5 ml (±22.53)	30.8 ml (±18.90)	71.6%	0.001
Non neuropathic bladder	92.1 ml (±16.46)	23.8 ml (±19.26)	74.1%	0.005
Total	100.3 ml(±13.53)	27.3 ml (±12.90)	72.8%	0.0001

Table 3: Response of the Maximum flow rate of urine.

Types	Pretreatment Mean Qmax(±Std. Error Mean)	Post treatment Mean Qmax(±Std. Error Mean)	Increase in Qmax rate %	P value
Neuropathic bladder	7ml/sec (±1.10)	18.5 ml/sec (±4.12)	62.1%	0.004
Non neuropathic bladder	6.25 ml/sec (±1.66)	23.8 ml/sec (±2.07)	73.7%	0.017
Total	6.65ml/sec (±0.96)	21.1ml/sec (±2.34)	68.4%	0.0001

DISCUSSION:

Voiding dysfunction is an important problem in childhood due to its relatively high prevalence.[18-20] and the fact that it may cause upper urinary tract deterioration with renal scarring.[21] There are several reports of α-blocker therapy in children with incomplete bladder emptying characterized by increased post-void residual, prolonged urine flow, and obstructive symptoms.[22,23]

In our study the response of 24 patients with voiding dysfunction to selective α-1 blocker was evaluated, to assess the true effectiveness of α-1antagonists in the

treatment of pediatric voiding dysfunction. The true effectiveness of α blocker in

the literatures is limited because the majority of patients involved in these studies have concurrently been treated with multiple medical and/or behavior modification therapies.[23,24]

Alph-1 blocker relaxed the bladder neck and led to improvement in the retention. This is supported by Perlberg and Caine who examined wall strips of unstable human bladders in the setting of bladder outlet obstruction and observed an α-adrenergic response.[25] Another possible explanation for improving of retention was done by Danuser and Thor reported that somatic efferent activity via the pudendal nerve decreases after the administration of the selective α-blocker, which may decrease external sphincter activity.[26] Restorick and Mundy reported an almost 4-fold increase in the density of α-adrenoreceptors in the detrusor tissue of the patients with bladder overactivity than in those with normal bladder activity. [27]Therefore the use of α-blocker may lead to the relaxation in the bladder neck allow the bladder to expel a large amount of urine.

The mean of maximum flow rate increased to 21.1 ml/sec (increased 68.4% and p= 0.0001). This result was inconsistence with Austin *et al* who had only 3 exhibitedincreased flow.[23] The alpha one receptors which are found in the proximal urethra in addition to that distributed in the bladder neck

permits the alpha blocker to improve the Qmax. However, substantial evidence supports action at the extraprostatic sites involved in micturition, including the bladder dome smooth muscle and this may represent an additional factor in the improvement of the maximum flow rate. [28]

Failure in relieving symptom occurred in 4 patients who had neuropathic dysfunction and presented with retention. Six patients (25%), "four of them were neuropathic and two were underactive bladder syndrome" failed in improved of PVR and Qmax in response to treatment with doxazocin. The causes of the failure seem to be that the voiding dysfunction was multifactorial . we need more study to compare the effect α- blocker alone and its effects when adding antimuscarinic.In Austin *et al* study The patients failed to treatment were hinman's syndrome,[23] whereas the patients with hinman's syndrome involved in our study respond well to doxazocin.

Our study adds further support to the evidence suggesting the role for alpha adrenergic blockade therapy in children with voiding dysfunction. The medication has been proven to be safe in children, and results in rapid and significant improvement in bladder emptying. The addition of this therapy early in management has the potential to eliminate the need for the more labor and time intensive biofeedback in some patients.

CONCLUSION:

From our result we conclude that selective alpha blocker seems to be effective for improving symptoms and bladder emptying in various pediatric voiding dysfunctions . Also it seems to be well tolerated in children.

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