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Effect of Tadalafil on Renal Resistivity and Pulsatility Index in Partial Ureteral Obstruction

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Key Words
Partial ureteral obstruction · Pulsatility index · Resistivity index · Tadalafil

Abstract
Introduction: To investigate the effect of tadalafil on Resistivity Index (RI) and Pulsatility Index (PI) in partial unilateral ureteral obstruction (PUUO). ***Methods:*** Twelve New Zealand rabbits were assigned into two groups. Baseline renal Doppler ultrasonography (USG) was performed in all rabbits. The rabbits in group 1 received tadalafil for a month (10 mg/72 h) and group 2 was defined as sham. After 1 month, in both groups left PUUO was created. Renal Doppler USG was performed to measure RI and PI parameters of both kidneys on the 4th hour and 1st and 3rd days postoperatively. ***Results:*** Baseline renal Doppler USG revealed that there was no difference between two kidneys in both groups. The differences in mean RI and PI values of the kidneys between the sham and tadalafil groups were not statistically significant. Compared with the preoperative values, postoperative RI and PI values for the left kidneys were significantly increased in the period from 4 h to 3 days postoperatively in the sham group ($p < 0.05$). However, mean RI and PI values were not increased in the tadalafil group when compared with the sham group and this difference between the two groups was significant ($p < 0.05$). ***Conclusions:*** Tadalafil has a lowering affect on RI and PI in experimentally created PUUO.

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Introduction

Partial unilateral ureteral obstruction (PUUO) causes reversible and irreversible destruction in kidneys and ureters. Renal blood flow impairment, intrapelvic pressure elevation, and vasoactive and inflammatory mediators are some of the known etiologic factors for renal obstructive parenchymal injury [1] and these factors can cause hypoxia and tissue ischemia.

Resistivity Index (RI) (peak systolic velocity – end-diastolic velocity/peak systolic velocity) and Pulsatility Index (PI) (maximum systolic velocity – minimum diastolic velocity/average velocity) measured by renal Doppler ultrasonography (USG) are the variables most widely used as hemodynamic parameters in the sonographic evaluation of presumed renal obstruction [2]. Although RI and PI are contributory parameters in the diagnosis of obstruction, they are noninvasive, easily used tests and can be safely used in pregnant women and in patients with contrast

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material allergy or chronic renal failure. Although there is still an uncertainty about the sensitivity of RI vs. PI values in estimating renal function, RI and PI values provide clinically important data about organ perfusion and resistance against blood flow in the vessel lumen [3].

Many drugs have been investigated for their efficacy on RI and PI in the literature and it has been stated that these drugs could attenuate renal injury during obstruction. Tadalafil, which is used for erectile dysfunction (ED), is a potent, selective and reversible phosphodiesterase 5 (PDE5) inhibitor. The PDE5 inhibitor causes smooth muscle relaxation [4] and according to our best knowledge of the literature the effect of tadalafil on PUUO has not been investigated previously. The purpose of this study was to investigate the effect of tadalafil on RI and PI in rabbits with normal ureters and with experimentally partially obstructed ureters.

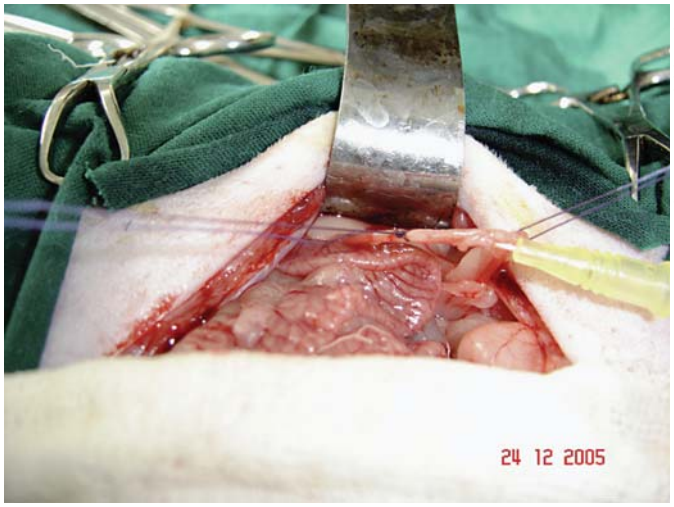

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Fig. 1. Left ureter after partial ureteral obstruction formation.

Material and Methods

The study included 12 New Zealand rabbits (6 sham, 6 tadalafil), weighing between 2,400 and 3,500 g (mean 2,800 g). The rabbits were randomly assigned into two experimental groups. At the beginning of the study, RI and PI values of both kidneys were measured in all rabbits with renal Doppler USG (Esaote Biomedica AU5®) by using a 7.5–10 MHz multifrequency linear probe.

The abdominal region of rabbits was shaved for a better image before USG and Doppler USG. Sedatives or anesthetics were not used since they can affect Doppler USG parameters. The renal shape, size and width, echogenicity of the parenchyma, and renal pelvis diameter were evaluated during renal USG and data were recorded.

Doppler signals were generally obtained from the interlobar arteries along the border of the medullary pyramids and from the arcuate arterioles along the corticomedullary border. Peak systolic and end-diastolic velocities of the arteries were recorded and the RI values were measured using built-in computerized calculations.

The rabbits in group 1 received tadalafil (Cialis®, Lilly, Indianapolis, Ind., USA) for 1 month. Tadalafil tablets were diluted with 10 ml distilled water to form a homogeneous solution. It was administered orally to rabbits at a dose of 10 mg/72 h, as the affect of tadalafil lasts for 72 h. Group 2 was defined as sham and received no drug. At the end of 1 month, renal USG and Doppler USG for RI and PI parameters were determined again in all rabbits before the rabbits underwent the surgical procedure.

Surgical Procedure

Xilasine (20 mg/kg i.m.) and ketamine HCl (50 mg/kg i.m.) were used for general anesthesia. Laparotomy, exposure and isolation of the left ureter in the tadalafil and sham groups was performed under general anesthesia. Left PUUO was created by placing a 24-gauge (19 × 0.7 mm) intravenous catheter into the proximal ureter and ligating the ureter and catheter around the ureter by using a 3–0 silk suture (fig. 1). The partial ureteral obstruction

Fig. 2. Left ureteral partial obstruction on excretory urography.

model has been defined in several methods [5–7]. In our study, we performed a new method to create PUUO. By ligating over the catheter, the ureters were narrowed surgically. The catheter was then removed cautiously so as not to injure the ureter and the abdominal incision was closed.

Postoperatively, excretory urography after the injection of 1.5 ml/kg of iopromide (Ultravist 370; Schering, Berlin, Germany) confirmed the presence of PUUO (fig. 2). Renal Doppler USG was also performed postoperatively by the same researcher in both kidneys at the 4th hour and the 1st and 3rd days.

Table 1. Summary of mean RI and PI in both groups

Group		Mean preoperative values				Mean postoperative values					
		baseline		1st month		4th hour		1st day		3rd day	
		L	R	L	R	L	R	L	R	L	R
Group 1 (T)	RI	0.49 + 0.01	0.48 + 0.02	0.50 + 0.02	0.51 + 0.02	0.52 + 0.02	0.48 + 0.01	0.46 + 0.02	0.48 + 0.02	0.49 + 0.02	0.49 + 0.02
Group 2 (S)	RI	0.50 ± 0.01 (0.485)	0.50 ± 0.01 (0.818)	0.50 ± 0.01 (0.699)	0.50 ± 0.01 (0.485)	0.64 ± 0.02 **(0.002)**	0.56 ± 0.02 **(0.009)**	0.62 ± 0.02 **(0.002)**	0.47 ± 0.02 (0.818)	0.54 ± 0.01 **(0.004)**	0.61 ± 0.01 (0.240)
Group 1 (T)	PI	1.41 ± 0.04	1.33 ± 0.02	1.47 ± 0.01	1.41 ± 0.06	1.44 ± 0.04	1.41 ± 0.04	1.37 ± 0.03	1.37 ± 0.04	1.37 ± 0.03	1.49 ± 0.04
Group 2 (S)	PI	1.46 ± 0.05 (0.589)	1.45 ± 0.04 (0.485)	1.43 ± 0.04 (0.065)	1.50 ± 0.03 (0.240)	1.73 ± 0.07 **(0.009)**	1.34 ± 0.04 (0.310)	1.55 ± 0.04 **(0.026)**	1.34 ± 0.03 (0.699)	1.60 ± 0.01 **(0.002)**	1.37 ± 0.02 (0.132)

R = Right kidney; L = left kidney; T = tadalafil; S = sham. Figures in parentheses are p values, bold indicating statistical significance.

Statistical Analysis

Statistical data were analyzed using Statistical Package for the Social Sciences (SPSS, Chicago, Ill., USA) version 13.0 for Windows. All values were expressed as mean ± SD. Differences between groups were compared by the Mann-Whitney U test. $p < 0.05$ was considered to indicate statistical significance.

Results

Twenty-four renal units were evaluated in 12 New Zealand rabbits. Baseline sonographic gray-scale examinations (renal length, width, cortical thickness and pelvic diameter) were in normal ranges in all the rabbits. Baseline renal Doppler USG revealed that there was no difference between two kidneys according to coloration due to perfusion in both groups. The mean RI values were between 0.48 and 0.50 and the mean PI values were between 1.33 and 1.46. The differences in mean RI and PI values of the left and right kidneys between sham and tadalafil groups were not statistically significant (p = 0.485 and p = 0.589, p = 0.818 and p = 0.485, respectively) (table 1).

The measurements were repeated at the end of the tadalafil treatment after 1 month and there was again no difference regarding the ultrasonographic findings between the two groups. RI and PI values of the left and right kidneys were again not different (p = 0.699 and p = 0.065, p = 0.485 and p = 0.240, respectively).

Following surgical procedures, all rabbits had developed various degrees of renal pelvic dilatation in the left kidney as early as 4 h. Similar to classical urologic knowledge about obstruction, renal pelvic dilatation and renal cortical echogenicity were increased progressively at repeated examinations.

RI and PI values of the left kidney were significantly decreased in the tadalafil group in comparison with the sham group at the 4th hour and 1st and 3rd days postoperatively (p = 0.002, p = 0.002, p = 0.004 for RI and p = 0.009, p = 0.026, p = 0.002 for PI). Interestingly, the RI value for the right kidney was decreased in the tadalafil group only at the 4th hour postoperatively (p = 0.009). However, this affect discontinued in the following days (table 1).

Discussion

Several methods have been investigated for diagnosing PUUO. RI and PI parameters, which can be measured with Doppler USG, are two of these methods. Although many studies on RI measurement and its efficacy can be found in the literature [8–14], the number of studies on PI is limited. These studies emphasize the diagnostic value of RI in PUUO. Platt et al. [10] reported that the RI will not be elevated until the obstruction continues for more than 5–6 h. Chen et al. [11] showed that the degree of obstruction can affect the renal RI value. Fung et al. [12] demonstrated an association between elevated renal RI value and high intrarenal pressure. The elevation in renal RI after PUUO is due to a decreased renal blood flow in the early stage and an increased vascular resistance in the kidney [13, 14].

Tadalafil is a selective, potent and reversible inhibitor of the PDE5 enzyme. PDE5 is shown to be widely distributed in the smooth muscles of vessels and internal organs, and striated muscles. The inhibition of PDE5 results in smooth muscle relaxation. Tadalafil also increases the nitric oxide (NO) level in tissue via PDE5 inhibition.

NO is a nonadrenergic and noncholinergic neurotransmitter. Nitric oxide synthase (NOS) is the responsible enzyme for the production of NO. In an experimental study with rats, after forming unilateral PUUO, the injection of L-N-monomethyl-arginine (L-NMMA), a nonselective NOS inhibitor, caused a decrease in renal blood flow and an increase in renal vascular resistance [15]. NO has been shown to be produced in acute unilateral ureter obstruction and to play an important role in renal hyperemia occurring during the early phase [16].

Until now, several chemicals and drugs such as diclofenac sodium, ketoprofen and furosemide have been investigated for their possible effects on RI in PUUO [17–21]. The inhibitor effects of nonsteroidal anti-inflammatory drugs on vasodilatation in the early phase and on vasoconstriction in the late phase can explain the effects of these drugs on RI at acute ureteral obstruction [19]. Hydration and diuretics affect the RI parameter by creating acute changes in renal pelvic pressure. The acute increase in urine formation after hydration and diuretic administration is thought to be responsible for the RI elevation [21]. In our study, we observed that the renal RI value was lowered in partially obstructed kidney by tadalafil administration ($p < 0.005$). This effect was probably due to the NO release that caused vasorelaxation and the decreasing hypoxia caused by the increasing perfusion. The main factors that cause an increase in RI value are decreased renal perfusion due to vasoconstriction and increased intrarenal vascular resistance. Another interesting point in our study was the decrease of RI and PI values that continued until the end of the third day, even though tadalafil had been stopped after the experimental partial obstruction.

An increase in intrarenal vascular resistance and a decrease in renal blood flow can be seen after PUUO formation. Biochemical mediators are responsible for the changes seen in renal blood flow. Many studies have investigated the roles of angiotensin II (AII), NO, endothelin and eicanoside (prostaglandins and thromboxanes) at acute and chronic changes in renal blood flow [22, 23]. NO has been reported to be effective in lowering preglomerular vascular resistance after ureteral occlusion. Many of the biologic actions of NO are mediated by cyclic 3′5′-guanosine monophosphate which is rapidly degraded by PDEs [24]. Thus, inhibiting PDEs with tadalafil elevated the NO level in tissue and the increased NO caused vasodilatation and increased perfusion in the ischemic regions.

It has been reported that RI and PI values are associated with each other [14, 25–27]. PI velocity values are more sensitive than RI; however, because there are concerns about obtaining an average velocity, this parameter is not used extensively. PI is an important parameter used specially in vascular diseases. In a prospective study, Yagcı et al. [28] reported that PI values played a contributory function for differentiating obstructive and nonobstructive conditions in children with ureteropelvic obstruction. Additionally, they stated that PI values are more independent than RI values when compared according to obstruction side and age variables.

Studies comparing RI and PI values in the pre- and post-PUUO periods are lacking in the literature. Until now, RI has been evaluated mostly in the diagnosis of PUUO. Additionally, nonsteroidal anti-inflammatory drugs and diuretics have been the most evaluated substances in the drug category. In our study, left renal PI values in the study group were significantly decreased in comparison with the sham group in all the postoperative measurements ($p < 0.005$, $p < 0.05$, $p < 0.005$) (table 1). This finding supports the beneficial use of the PI in addition to RI in the diagnosis of obstruction.

Conclusions

We evaluated the effect of tadalafil on RI and PI in PUUO and found that this drug has a lowering effect on these parameters. In our opinion, these findings can lead to use of this drug to minimize the poor affects of obstruction in clinical practice. However, experimental studies that include renal function and placebo-controlled clinical studies with long-term follow-up and large numbers are needed to support our findings.

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