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RESEARCH ARTICLE

Comparison of Excretory Urography, Ultrasonography-Guided Percutaneous Antegrade Pyelography, and Renal Doppler Ultrasonography in Rabbits with Unilateral Partial Ureteral Obstruction: An Experimental Study

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Summary

The aim of this study was to compare diagnostic efficiency of excretory urography (EU), ultrasonography-guided percutaneous antegrade pyelography (UGPAP), and renal Doppler ultrasonography (DUS) in New Zealand rabbits (n= 20) experimentally induced unilateral partial ureteral obstruction. The resistive index (RI) value was obtained from all rabbits prior to the induction. A partial ureteral obstruction was created on the left ureter by laparotomy in all rabbits. Applications of direct renal DUS and renal DUS after furosemide administration were performed on days 1 and 10 post-operation. Rabbits were divided into two groups. Rabbits in the first group were subjected to EU, whereas those in the second group were subjected to UGPAP. The obstructive point was successfully determined all rabbits in the EU group on both days 1 and 10 post-operation, whereas in 8 rabbits on day 1 post-operation and all rabbits on day 10 post-operation in the UGPAP group. On both measurements, the mean RI values of the obstructed and non-obstructed kidneys were different (0.567 vs. 0.494; P<0.001). The RI value of non-obstructed kidneys decreased further with furosemide administration. The mean RI difference (RIΔ) after furosemide administration increased. In conclusion, in addition to EU and UGPAP, commonly used imagining methods in veterinary medicine, renal DUS after diuretic administration should be performed as a non-invasive technique to increase diagnostic efficiency of unilateral partial ureteral obstruction.

Keywords: *Renal Doppler ultrasonography, Excretory urography, Ultrasonography-guided percutaneous anterograde urography, Unilateral partial ureteral obstruction, Rabbit*

Tavşanlarda Unilateral Parsiyel Üreteral Obstruksiyonda Ekskretör Ürografi, Ultrason Rehberli Perkutan Anterograd Pyelografi ve Renal Doppler Ultrasonografi Tanı Yöntemlerinin Karşılaştırılması: Deneysel Çalışma

Özet

Bu çalışmada, unilateral parsiyel üreteral obstruksiyon şekillendirilen Yeni Zellanda tavşanlarda (n= 20) ekskretör ürografi (EÜ), ultrason rehberli perkutan anterograd pyelografi (UGPAP) ve renal Doppler ultrasonografi (DUS) tanı yöntemlerinin karşılaştırılması amaçlanmıştır. Resistive indeks (RI) değeri, obstruksiyon şekillendirilmeden önce bütün tavşanlarda elde edildi ve laparatomi yapılarak tavşanların sol üreterlerinde parsiyel üreteral obstruksiyon oluşturuldu. Post-operatif 1. ve 10. günlerde bütün tavşanlara direkt renal DUS ve furosemid uygulaması sonrası DUS yapıldı. Tavşanlar onarlı iki gruba ayrıldı. Birinci gruba EÜ, ikinci gruba ise UGPAP yapıldı. İki farklı zamandaki EÜ grubunda bütün tavşanlarda; UGPAP grubunda ise 1. günde 8 tavşanda, 10. günde ise bütün tavşanlarda obstruktif odak belirlendi. Her iki ölçüm zamanında obstruktif böbreğin ortalama RI değeri (0.567) ile non-obstruktif böbreğin ortalama RI değerinde (0.494) arasında fark vardı (P<0.001). Non-obstruktif böbreğin RI değeri furosemid uygulaması ile daha da azaldı. Furosemid uygulaması sonrasında ortalama RI farkı (RIΔ) arttı. Sonuç olarak; unilateral parsiyel üreteral obstruksiyonun tanısında, Veteriner Hekimlikte yaygın olarak kullanılan EÜ ve UGPAP tanı yöntemlerinin yanı sıra non-invaziv bir yöntem olan renal DUS'nin, diüretik uygulaması ile tanı yöntemi olarak kullanılabileceği kanısına varıldı.

Anahtar sözcükler: *Renal Doppler ultrasonografi, Ekskretör ürografi, Ultrason rehberli perkutan anterograd ürografi, Parsiyel unilateral üreteral obstruksiyon, Tavşan*

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INTRODUCTION

Ureteral obstruction is one of the most important urinary system pathologies caused by a number of factors and may lead to kidney failure [1] characterized by irreversible and reversible destructions in kidneys and ureters [2]. Etiological factors can be categorized as congenital, acquired, and predisposing factors [3]. In addition to the discrimination of obstructive and non-obstructive dilatation, it is also imperative to determine localization and extent of the obstructed area in order to avoid unnecessary surgical intervention [4,5]. The early diagnosis and release of obstruction are critical for preventing irreversible damages in affected kidneys [6]. In diagnosis of ureteral obstruction, various imaging methods are used, such as radiography, excretory urography (EU), ultrasonography (US), Doppler ultrasonography (DUS), computer tomography (CT), magnetic resonance imaging (MRI) and percutan antegrade pyelography [7,8]. Excretory urography and renal US are routinely used in evaluating urinary system [6]. Excretory urography is a type of contrast study used to verify and localize urinary tract disease. In some instances, information regarding renal function and disease pathophysiology can also be obtained [9].

Until recently, it has been reported that none of the imaging methods has capability to evaluate the urinary system both anatomically and physiologically [6]. Although conventional grey-scale US provides only an anatomical depiction of the changes in ureteral obstruction, employment of DUS in obstruction cases provide comprehensive information about kidney diseases and indicate renal morphology as well as changes in renal blood flow under different pathophysiological conditions. Substantial changes in the intrarenal arterial Doppler waveform are associated with various pathological conditions. The intrarenal RI calculated as [(peak systolic velocity - end diastolic velocity)/peak systolic velocity], is the most commonly used variable to quantify changes in intrarenal Doppler waveforms [10].

The objective of this experiment was to compare diagnostic efficiency of EU, UGPAP, and renal DUS in rabbits induced-unilateral partial ureteral obstruction at early stage.

MATERIAL and METHODS

Animals, Management, Experimental Groups

The Animal Care Ethics Committee of Ankara University, Veterinary Faculty, Turkey, approved the study. A total of 20 mature male New Zealand rabbits weighing 2.48-3.24 kg were housed at 25°C, with a 12-h dark/light cycle. They were fed standard rat chow and had free access to water.

After applications of direct renal DUS and renal DUS following furosemide administration (1 mg/kg, IV, Lasix®, Aventis, Turkey) on days 1 and 10 post-operative, rabbits were divided into two groups: Those subjected to EU and UGPAP. To determine basal RI value, direct DUS was applied on all rabbits a day prior to induction of unilateral ureteral obstruction.

Surgical Procedure

All rabbits were undergone laparotomy under general anesthesia with (5 mg/kg IM, Xylazine HCl, Rompun®, Bayer, Turkey and 40 mg/kg IM, Ketamine HCl, Ketalar®, Pfizer, Turkey). After exposure and isolation of the left ureter, the partial ureteral obstruction was induced by inserting an 24-gauge intravenous catheter (0.7 mm-diameter) from outside lumen to inside lumen of the left proximal ureter and ligating the ureter from outside lumen by using a 3-0 silk suture, and then leaving the silicon part of the catheter out of the ureter lumen [11]. All rabbits were subcutaneously injected with penicillin-G (Iecilline®, IE Ulugay, Turkey) for 3 days after operation (60 U/kg/d).

Ultrasonographic and Doppler Ultrasonographic Measurements

A linear probe with a multifrequency feature (7.5-10 MHz) was used in US and DUS (ESAOTE, AU5 model, Esaote Biomedica, Genova, Italy). Kidney morphology was evaluated at the dorsal, longitudinal, and transversal planes during ultrasonography. The wall filter and sample volume were kept at minimum during renal DU. Measurements were made at 60° angle. Spectral samples were made on arteries (aa. arcuatae and aa. interlobares) located at three different points of the kidney during pre- and post-operative stages as well as before and after diuretic administration for Duplex Doppler evaluation. The RI value was estimated using the peak systolic velocity and end diastolic velocity after compiling similar wave forms (n=3-5) from arteries. RI difference (RIΔ) defined using the formula: RIΔ = RI of obstructed kidney - RI of non-obstructed kidney.

Excretory Urography and Ultrasonography-Guided Percutaneous Antegrade Pyelography

The lateral and ventrodorsal abdominal radiographies were taken at 5, 10, 20, and 40 min after the rapid delivery of a non-ionic contrast agent (Iopromide, 1.5 ml/kg, Ultravist 370®; Schering, Germany) through the cephalic vein in the EU group.

Under general anesthesia, after slow administration of propofol (10 mg/kg, IV, Pofol®, Sandoz, Turkey), ultrasonography-guided percutaneous antegrade pyelography was performed in the UGPAP group. Some urine was removed from pelvis renalis, by entering the kidney percutaneously under guidance of ultrasonographic imaging at the dorsal plane. After replacing volumetric loss of urine with the same non-ionic contrast agent, the laterolateral and ventrodorsal abdominal radiographies were taken.

Data Analysis

The mean RI values, differences between measurement times and between obstructed and non-obstructed kidneys and RIΔ were compared using t-test and 2-way ANOVA with repeated measures option (SPSS, Version 10.0.0, Chicago, IL). The statistical significance was declared at P<0.05.

RESULTS

Kidney Morphology

Pelvis renalis, dilated ureter, obstructed area, and distal ureter in the obstructed kidney were visible in the EU *(Fig. 1A)* and UGPAP *(Fig. 1B)* groups, on days 1 and 10 post-operation. Their appearances were clearer in the UGPAP group than in the EU group due to higher opacity. The obstructed area in the left ureter on days 1 and 10 was apparent in all rabbits subjected to EU. In the UGPAP group, the obstructed area in the left ureter was however determined in 8 rabbits on day 1 and all rabbits on day 10 post-operation. In two cases, it was also noted that the contrast matter leaked into the abdominal cavity on day 1 post-operation.

Forty renal units were evaluated in 20 New Zealand rabbits by US. Basal grey-scale US examinations (renal length, width, cortical thickness and pelvic diameter) were in normal ranges in all the rabbits. Basal renal DUS revealed that there was no difference between two kidneys according to coloration due to perfusion.

Ultrasonography on day 1 post-operation revealed mild hydroureter and hydronephrosis in 15 rabbits both groups *(Fig. 2)*. These pathologies became moderate in all rabbits in both groups on day 10 post-operation, with a slight increase in dimension of the obstructed kidneys.

Renal RI and RIΔ

The threshold RI level for ureteral obstruction (0.70) was exceeded in neither on day 1 nor 10 post-operation in all rabbits. The RIΔ exceeded the threshold level (0.11) in 2 rabbits on day 1 post-operation and 3 rabbits on day 10 post-operation after direct DUS and in 6 rabbits on day 1 post-operation and 8 rabbits on day 10 post-operation after furosemide administration + DUS *(Fig. 3)*. The mean values for RI at left kidney (RIl) and RI at right kidney (RIr) were 0.51±0.04 vs. 0.509±0.04 at baseline (t = -0.24, P<0.82); 0.565±0.063 vs. 0.501±0.06 on day 1 (t = -0.57, P<0.001) and 0.628±0.048 vs. 0.526±0.038 on day 10 (t = -8.19, P<0.0001) after direct DUS; and 0.597±0.055 vs. 0.473±0.041 on day 1 (t = -9.79, P<0.0001) and 0.597±0.049 vs. 0.447±0.054 on day 10 after furosemide administration + DUS (t = -8.77, P<0.0001), respectively.

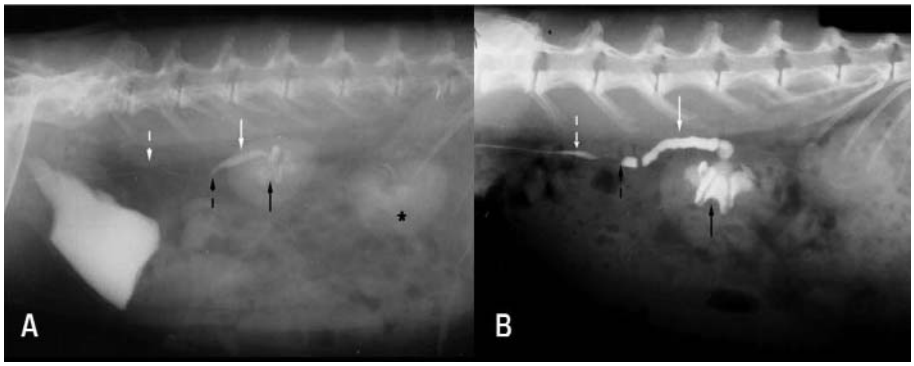

Fig 1. ***A-*** The left-lateral radiogram of the left and right kidney (*) at 20th min of excretory urography performed on day 10 post-operation. ***B-*** The left-lateral radiogram of the left kidney at the 5th min of ultrasonography-guided percutanous antregrade pyelography conducted on day 10 post-operation. A dilated pelvis renalis in the left kidney (black arrow); a dilatation in the left ureter (white arrow); the obstruction point (broken black arrow) and the left distal ureter (broken white arrow)

Şekil 1. ***A-*** Postoperatif 10. günde yapılan EU uygulamasının 20. dakikasında alınan sol ve sağ böbreğinin (*) görüntülendiği sol lateral radyogram. ***B-*** Postoperetif 10. günde yapılan URPAP uygulamasının 5. dakikasında alınan sol böbreğin görüntülendiği sol lateral radyogramı. Sol böbrekte dilate pelvis renalis (siyah ok), sol üreterde dilatasyon (beyaz ok), obstruksiyon noktası (kesikli siyah ok) ve sol distal üreter (kesikli beyaz ok) izlenmektedir

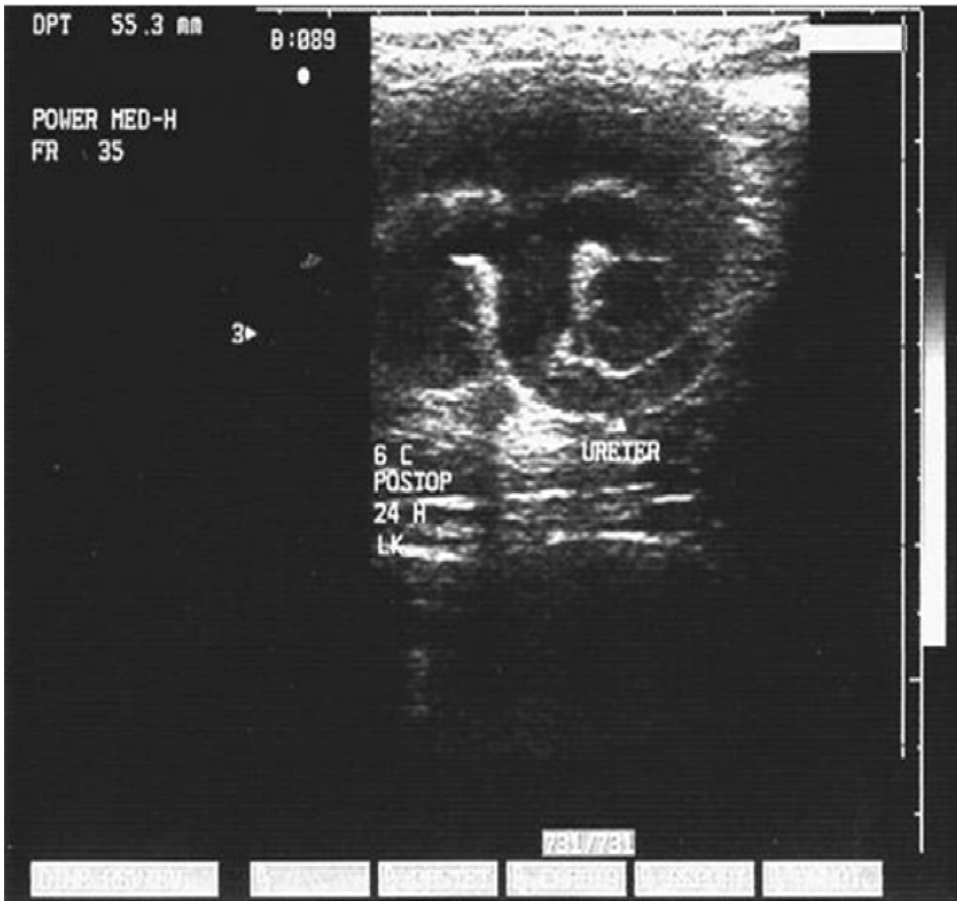

Fig 2. The image of left kidney, dilated pelvis renalis and hydro-ureter 24 h after operation

Şekil 2. Postoperatif 24. saatte sol böbreğin, dilate pelvis renalisin ve hidro-üreterin görünümü

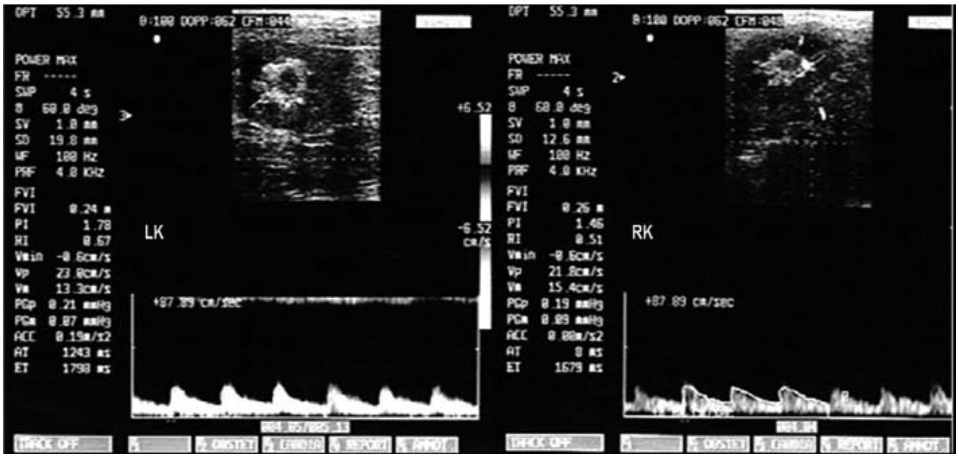

Fig 3. The duplex Doppler ultrasonographic image of the left and right kidney on day 10 post-operation after furosemide administration. The RIΔ is 0.16

Şekil 3. Postoperatif 10. günde Furosemid uygulaması sonrası sol ve sağ böbreğin dupleks Doppler US görüntüsü. RİΔ, 0.16 olarak izlenmektedir

The RIl value upon direct DUS and furosemide administration + DUS was not different (0.567±0.008). As time progressed, RIl values continuously increased from 0.511 to 0.610 (P<0.0001), but this increase was independent from the groups (*Fig. 4A;* P>0.05).

The RIr value obtained upon direct DUS was greater than that obtained upon furosemide administration + DUS (0.513 vs. 0.476, P<0.003). The RIr values remained constant (0.494±0.01) over time. There was a group by time interaction effect on RIr value (*Fig. 4B;* P<0.04); it was constant over time upon direct DUS, whereas it continuously decreased over time upon furosemide administration + DUS.

The RIΔ was lower upon direct DUS was greater than upon furosemide administration + DUS (0.064 vs. 0.094, P<0.004). RIΔ also increased quadratically from 0.014 to 0.123 as the monitoring period advanced (P<0.0001). This increase tended to be at a greater extent upon furosemide administration + DUS than direct DUS (*Fig. 4C;* P<0.08).

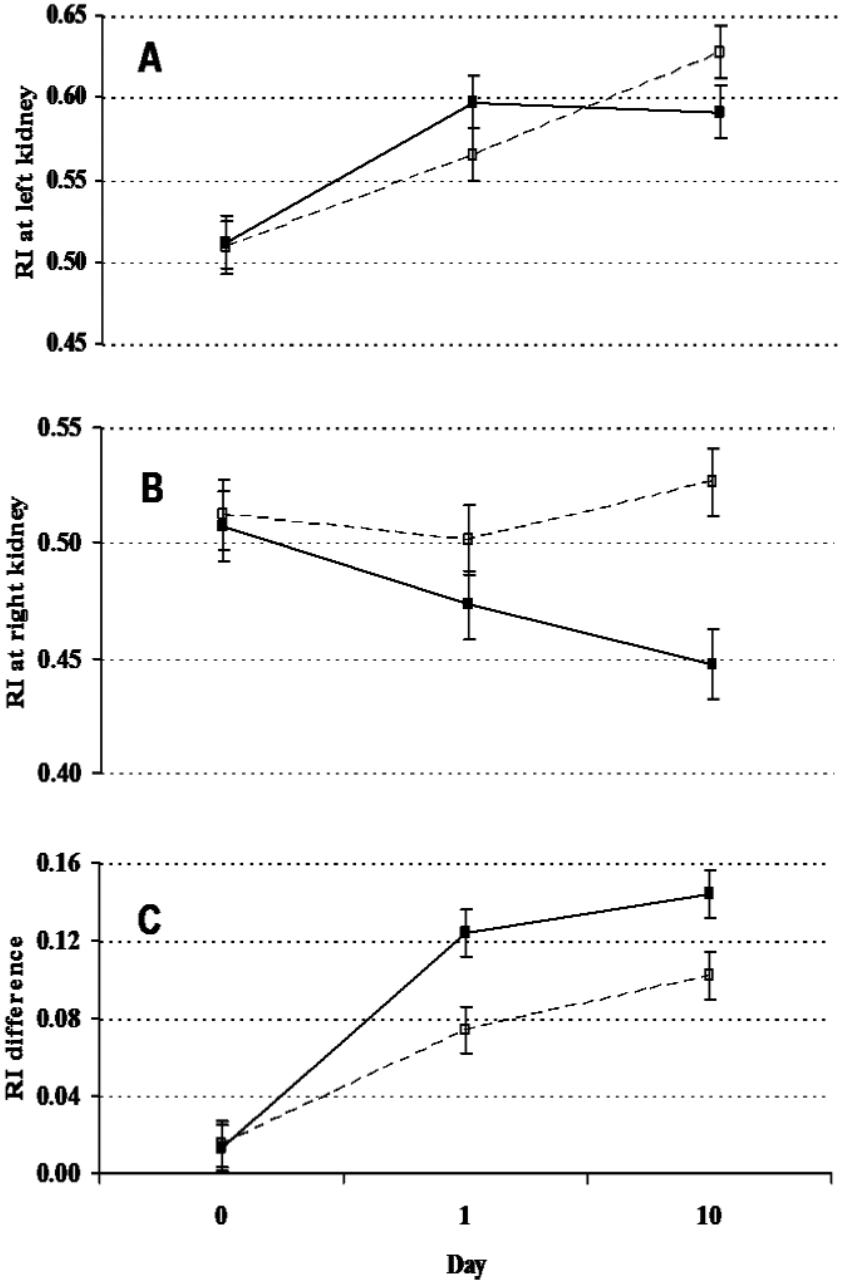

Fig 4. ***A*****-** There was no intervention by time interaction effect on RIl (P>0.05); ***B*****-**There was intervention by time interaction effect on RIr (P<0.04); ***C*****-** There was intervention by time interaction trend on RIΔ (P<0.08). (□; direct DUS vs. ■; DUS after furosemide administration)

Şekil 4. ***A*****-** RIl'de zaman bağlı olarak karşılıklı etkileşim izlenmedi (P>0.05); ***B*****-** RIr'da zaman bağlı olarak karşılıklı etkileşim izlendi (P<0.04); ***C*****-** RIΔ'da zaman bağlı karşılıklı etkileşim eğilimli olarak izlendi (P<0.08). (□; direkt DUS vs. ■; furosemid uygulaması sonrası DUS)

DISCUSSION

Despite biomedical advancement, diagnosis of the ureteral obstruction is still difficult. In veterinary medicine, EU is frequently applied to view the urinary system and diagnose the ureteral obstruction [6], thank to its sophisticated design that provides information about the renal vascular structures, kidney shape and dimension, and renal collector elements [12]. However, its application is limited due to sensitivity to ionic contrast agent that could cause allergic reactions and even anaphylaxis shocks as well as nephropathy in diabetic and hypertensive geriatric patients. Its application is totally harmful in patients with uremia [13-15] and may not provide enough opacity on kidney collector elements to evaluate the urinary system in patients with renal dysfunction [16]. Therefore, in renal disease, contrast media for optimal image must be administered in double or threefold of normal dosage, which may increase risk for iatrogenic renal damage [17]. Excretory urography was employed to determine position and shape of kidneys, pelvis renalis, and ureter in the present experiment. In two measurement times, obstructive point was successfully determined. In particular, imaging pelvis renalis and ureter possessed enough quality due to opacity, which could be related to being obstruction partial and short term that might cause damage in parenchyma.

Percutanous antegrade pyelography under guidance of ultrasonography and/or fluoroscopy is commonly facilitated in veterinary diagnosis. Its advantages include determination of location of the obstructive area, prevention of side effects caused by systemic contrast matter, and achievement of image of pelvis renalis and ureter in patients with kidney failure. However, it is an invasive method and difficult to perform as well as requires anesthetic administration. Moreover, there are also possibilities of 1) development of hematuria, 2) obstruction due to the leakage of blood into pelvis renalis and 3) urine accumulation in the peritoneal cavity due to the leakage [8,18]. In this experiment, images of pelvis renalis and ureters via UGPAP were clearer than those via EU, possibly linked to accumulation of ionic contrast matter at certain locations. Comparing with via EU, it took shorter to determine the obstructed points via UGPAP. As experienced in this experiment, there might be likelihoods of failure due to allocating injection site due to absence of acute dilatation in pelvic renalis (n= 2).

Grey-scale US is a sensitive and non-invasive method for diagnosing dilatation in pelvis renalis due to obstructions (e.g., stone and lesion). However, it may not be feasible in the diagnosis of obstructions not accompanied by a dilatation and likely to fail in the discrimination of obstructive and non-obstructive dilatations [19,20]. No difficulty was experienced in the present study while evaluating kidney morphology and ureteral dilatation with US, but it was noted that ultrasonographic evaluation was not competent in 5 cases not developing pelvis renalis dilatation.

Doppler waveform studies are noninvasive, painless, readily available, and relatively easier to perform and learn. In addition, DUS obviates the need for ionizing radiation and intravenous contrast material administration in situations such as when they may be undesirable due to allergy and renal insufficiency. Because it has potential to detect kidney disease associated with increased or decreased resistance of the intrarenal vasculature, renal blood flow can be assessed indirectly by DUS measuring RI [19]. In normal individuals the intrarenal RI is ≤0.70 [10]. In the cases of ureteral obstruction, the RI value is ≥0.70 [21]. These suggest that measuring RI value enables DUS to have clinically excellent sensitivity and specificity in determining the presence or absence of obstruction in patients with calyceal dilatation. However, there are cases of mild ureteral obstruction with an intrarenal RI of ≤0.70 [19]. Moreover, intrarenal RI value may be inadequate in diagnosing partial ureteral obstruction [22,23]. In the present experiment, although rabbits with partial ureteral obstruction attained a post-operative obstructed kidneys RI values higher than pre-operative RI values, all values never reached the threshold of 0.70. The RI values of obstructed kidney on day 1 post-operation were higher than those measured on day 10 post-operation in direct measurement.

Diuretic DUS is a modification of conventional DUS that exploits the physiological responses of obstructed and non-obstucted kidneys to diuretic stimulation [4,24]. To improve the sensitivity of intrarenal RI measurement for detecting mild but functionally significant ureteral obstruction, specialized techniques using diuretic stimulation have been developed [4,25,26]. Furosemide provocation leads to increases in the RI of obstructed kidneys, while having no effect on non-obstructed kidneys in adults and children [4,24]. Studies have also shown that saline loading with furosemide provocation causes a divergent response; the RI value increases in the obstructed kidneys and decreases in the non-obstructed kidneys decrease [24,27]. In the present study, while the RI values of obstructed kidneys increased upon furosemide administration on day 1 post-operation and decreased upon furosemide administration on day 10 post-operation. Also, the RI values of non-obstructed kidneys continuously decreased upon furosemide administration during the post-operation period *(Fig. 4A, B)*.

The intrarenal RI difference between non-obstructed and obstructed kidneys being equal to or greater than 0.11 indicates unilateral obstruction. This value enhances the sensitivity and specificity of Doppler studies, and enables the detection of obstruction in kidneys with bilaterally elevated baseline RI values, as in cases of renal medical disease or when the RI has yet reached the threshold value of 0.70 [21,28]. In DUS, delivering diuretics enhances diagnostic efficiency of partial obstruction, because they stimulate the RIΔ [18]. In renal DUS conducted on days 1 and 10 post-operation, there were 2 and 3 rabbits, respectively, had the RIΔ exceeding the threshold reference. After diuretic administration, the mean RI value of obstructed kidney increased on day 1 post-operation and that of non-obstructed kidney decreased during the post-operation period. Therefore, the RIΔ after diuretic administration increased, by 50 and 70% on days 1 and 10 post-operation, respectively *(Fig. 4C)*. Moreover, diuretic administration on day 1 post-operative was associated with an increase the RIΔ (≥0.11) in 3 of 5 cases that were free of hydronephrosis.

In conclusion, our data ascertained the superiority of renal DUS over other methods (EU and UGPAP), in terms of being non-invasive and cost-efficient, not necessitating ionized radiation usage and being executed in a shorter

time. The diuretic administration enhanced diagnostic efficiency of DUS in unilateral partial ureteral obstruction, magnifying the RIΔ. In some instances, UGPAP can be employed as well, because of providing high opacity.

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