Delayed Therapeutic Response Time Predicts Renal Damage in the First Episode of Febrile Urinary Tract Infection

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Objective: *To evaluate the relationship of therapeutic delay time (TDT) and therapeutic response time (TRT) with renal damage in the first episode of febrile urinary tract infection (UTI).*
Material and Method: *A prospective study was conducted in 67 children with the first episode of UTI at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital between 2008 and 2010. To assess for renal damage, dimercaptosuccinic acid (DMSA) renal scintigraphy was performed at one and six months after the acute episode.*
Results: *Abnormal DMSA renal scintigraphy was detected in 20 (29.9%) patients. There was no difference in TDT but TRT was different between the patients with normal and abnormal DMSA renal scintigraphy at p-value 0.001. The area under receiver operating characteristic (ROC) curve for TRT was 0.76 (95% confidence interval (CI) 0.64-0.86) at p-value 0.001. The optimal cut-off value for TRT was 22 hours with sensitivity 80.0% (56.3-94.1) and specificity 63.6% (47.8-77.6). In 50 patients with no vesicoureteral reflux (VUR), there was difference in TRT at p-value 0.002. The area under ROC curve for TRT was 0.82 (95% CI 0.69-0.96) at p-value 0.004. The optimal cut-off value for TRT was 25 hours with sensitivity 88.9% (95% CI 51.7-98.2) and specificity 68.4% (95% CI 51.3- 82.5).*
Conclusion: *TRT at or more than 22 hours predicts renal damage after first episode of UTI. In patients with no VUR, TRT at or more than 25 hours predicts renal damage. DMSA renal scintigraphy in the first episode of UTI should be considered in these patients.*

Keywords: *DMSA renal scintigraphy, Renal damage, Urinary tract infection*

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Urinary tract infection (UTI) that involves the renal parenchyma may result in acute or chronic renal damage, which may lead to hypertension, toxemia during pregnancy, impair renal function and even end stage renal disease[1]. The main risk factors in the development of renal scarring have been reported such as sex, age at onset, duration between diagnosis and the initiation of antibiotic treatment, virulent bacterial strains, recurrent infection, presence and severity of vesicoureteral reflux (VUR)[2-4]. Several conventional clinical presentations and laboratory investigations are used to differentiate lower tract from the involvement of renal parenchyma. However, none of these results can perfectly predict renal damage. Renal cortical scintigraphy with technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) is the most sensitive technique compared to the ultrasonography and the intravenous pyelography (IVP) for renal parenchymal change and renal scarring investigation[5]. Therapeutic delay time (TDT) had been reported in predicting abnormal DMSA renal scintigraphy in patients with the first febrile UTI[6-9]. However, Hewitt et al[10] reported that early treatment of acute pyelonephritis in children failed to reduce renal scarring. Longer TDT in the presence of non-refluxing and refluxing UTI had been reported in predicting acute renal cortical scintigraphic lesion and ultimate scar formation in patients with the first febrile UTI[7]. Therapeutic response time (TRT) had been reported in predicting abnormal DMSA renal scintigraphy in patients with the first febrile UTI, which were done within one week of their hospital admission[6,8]. However, TRT had not been reported in predicting renal damage and TRT in the presence of non-refluxing and refluxing UTI had not been reported in predicting abnormal DMSA renal scintigraphy and renal damage in the first episode of UTI.

The aim of the present study was to evaluate the relationship of the TDT and TRT with abnormal DMSA renal scintigraphy in the first episode of UTI.

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Material and Method

A prospective study of 67 hospitalized children with first episode of febrile UTI was done between January 2008 and December 2010 at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University. The inclusion criteria were patients who were admitted to pediatric in-patient services with the first episode of febrile UTI. First episode of febrile UTI was defined by first time UTI with fever (body temperature at or more than 37.8°C). Prior enroll to the study, patients with history of neurogenic bladder, previous episode of UTI, antibiotic treatment for the current UTI, or patients whose urine culture failed to become positive were excluded from the study. Voiding cystourethrography (VCUG), renal ultrasonography, and DMSA renal scintigraphy were performed in all patients. UTI was defined by growth of at least 10^5 colony-forming units per milliliter of a single bacterial species from midstream or catheterized urine specimens. Data collection included age, sex, TDT, TRT, VCUG, renal ultrasonography, and DMSA renal scintigraphy results. TDT was the number of days since the onset of fever until the first dose of antibiotic administration. TRT was the number of hours since the first dose of antibiotic administration until the resolution of fever (body temperature at or less than 37.5°C), when the patient was off antipyretics[6].

DMSA renal scintigraphy was performed at 1 and 6 months after the first episode of UTI with a gamma camera equipped with a low-energy, high-resolution collimator 2-3 hours following intravenous injection of a dose of 111 MBq (3 mCi) of ^{99m}Tc-DMSA according to the Paediatric Committee of the European Association of Nuclear Medicine's recommendations[11]. The authors did not repeat DMSA renal scintigraphy when the DMSA renal scintigraphy was normal at 1 month after UTI. Image interpretation was considered in terms of renal size, relative uptake function, uniformity of renal uptake, with single or multiple cortical defects, and associated contraction or volume loss in the involved cortex. Abnormal DMSA renal scintigraphy was interpreted as focal or multifocal perfusion defects or as a split renal uptake of less than 45%[5,11,12]. Informed consent was given by all parents of the children participating in the study. The present study was approved by the Ethics Committee at our institution.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, Illinois). Descriptive statistics were reported as mean, standard deviation (SD) or median (range) for continuous variables, and frequency and percentage for categorical variables. For categorical data, Chi-square test or Fisher's exact test was used to compare between normal and abnormal DMSA renal scintigraphy. For quantitative data, independent t-test or Mann-Whitney U test was used to compare between normal and abnormal DMSA renal scintigraphy as appropriate. The diagnostic test evaluation was calculated by receiver operating characteristic (ROC) curve analysis with 95% confidence interval (CI). A *p*-value of less than 0.05 was considered to be statistically significant.

Results

Sixty-seven children with first episode of febrile UTI were included in the present study. Eighty-two point one percent of them (43 boys and 12 girls) were less than 1 year of age, 17.9% of them (three boys and nine girls) were at or more than one year of age. Renal ultrasonography showed abnormalities in 23 (34.3%) patients. Abnormal DMSA renal scintigraphy at 1-month after UTI was detected in 20 (29.9%) patients. There were nine (45%) boys and 11 (55%) girls represented 19.6% in boys and 52.4% in girls. Table 1 presented demographic and laboratory data compared with DMSA renal scintigraphy results at 1-month after UTI. Girls were found to have more abnormal DMSA renal scintigraphy than boys at *p*-value 0.006. The median age for normal and abnormal DMSA renal scintigraphy group were 0.33 years (range 0.02-2.95 years) and 0.87 years (range 0.25-7.26 years), respectively. There was difference in median age between normal and abnormal DMSA renal scintigraphy at *p*-value less than 0.001, but no difference in TDT at *p*-value 0.96. However, there was difference in VUR and TRT between normal and abnormal DMSA renal scintigraphy at *p*-value less than 0.001 and 0.001, respectively.

ROC curve analysis was used to compare the diagnostic performance of TDT and TRT between normal and abnormal DMSA renal scintigraphy. The area under ROC curve for TDT were 0.51 (95% CI 0.34-0.67) at *p*-value 0.95. The result showed that TRT could predict normal and abnormal DMSA renal scintigraphy with accuracy. Fig. 1 showed the ROC curve for TRT when comparing the patients with normal and abnormal DMSA renal scintigraphy at 1 month after UTI. The area under ROC curve for TRT was 0.76 (95% CI 0.64-0.86) at *p*-value 0.001.

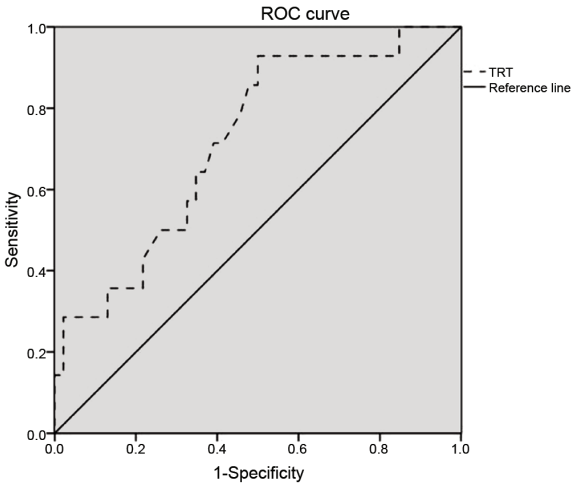

Fig. 1 ROC curve for TRT comparing the patients with normal and abnormal DMSA renal scintigraphy at 1 month after UTI. Area under ROC curve for TRT was 0.76 (95% CI 0.64-0.86, *p*-value 0.001).

The optimal cut-off value for TRT was 22 hours with sensitivity 80.0% (56.3-94.1) and specificity 63.6% (47.8-77.6).

All patients received VCUG. There were 50 (35 boys and 15 girls) with no VUR, and 17 (11 boys and six girls) VUR patients. In no VUR group, 44 patients were less than one year of age and six patients were at or more than one year of age. Forty-one (82%) patients had normal DMSA renal scintigraphy and nine (18%) patients had abnormal DMSA renal scintigraphy. In VUR patients, 11 patients were less than one year of age and six patients were at or more than one year of age. Six (35.3%) patients had normal DMSA renal scintigraphy and 11 (64.7%) patients had abnormal DMSA renal scintigraphy. Table 2 presented the impact of TRT on DMSA renal scintigraphy in non-refluxing and refluxing patients. In no VUR group, there was difference in TRT between normal and abnormal DMSA renal scintigraphy at *p*-value 0.002. In VUR group, there was no difference in TRT between normal and abnormal DMSA renal scintigraphy at *p*-value 0.313.

ROC curve analysis was used to compare the diagnostic performance of TRT in no VUR group between normal and abnormal DMSA renal scintigraphy. The results showed that TRT could predict normal and abnormal DMSA renal scintigraphy with accuracy. Fig. 2 showed the ROC curve for TRT in no VUR group when comparing the patients with normal and abnormal DMSA renal scintigraphy at 1-month after UTI. The area under ROC curve for TRT was 0.82 (95% CI 0.69-0.96) at *p*-value 0.004. The optimal cut-off value for TRT was 25 hours with sensitivity 88.9% (95% CI 51.7-98.2) and specificity 68.4% (95% CI 51.3- 82.5).

There were 17 out of 20 patients who had abnormal DMSA renal scintigraphy at 1-month

Table 1. Demographic and measured parameters compared with DMSA renal scintigraphy results at 1 month after UTI

Parameters	Total (n = 67)		*p*-value
	Normal DMSA (n = 47)	Abnormal DMSA (n = 20)	
Sex (boy/girl)	37/10	9/11	0.006*
Median age (years)	0.33 (0.02-2.95)	0.87 (0.25-7.26)	<0.001*
VUR	6 (12.76%)	11 (55%)	<0.001*
TDT (days)	2 (1-7)	2 (1-7)	0.96
TRT (hours)	14 (1-90)	36 (5-128)	0.001*

DMSA = dimercaptosuccinic acid; VUR = vesicoureteral reflux; UTI = urinary tract infection; TDT = therapeutic delay time; TRT = therapeutic response time
* *p*-value <0.05 for normal vs. abnormal DMSA

Table 2. Impact of each parameter on DMSA renal scintigraphy in no VUR and VUR patients

	No VUR (n = 50)			VUR (n = 17)		
	DMSA+ (n = 9)	DMSA- (n = 41)	*p*-value	DMSA+ (n = 11)	DMSA- (n = 6)	*p*-value
TDT (days)	2 (1-6)	2 (1-7)	0.692	2 (1-7)	2 (1-3)	0.750
TRT (hours)	45 (16-96)	14 (1-160)	0.002*	30 (5-128)	22 (4-54)	0.313

DMSA = dimercaptosuccinic acid; DMSA+ = abnormal DMSA; DMSA- = normal DMSA; VUR = vesicoureteral reflux; TDT = therapeutic delay time; TRT = therapeutic response time
* *p*-value <0.05 for normal vs. abnormal DMSA

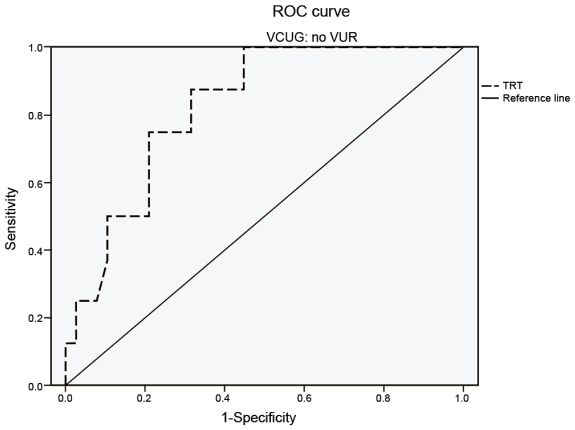

Fig. 2 ROC curve for TRT in no VUR patients comparing patients with normal and abnormal DMSA renal scintigraphy at 1 month after UTI. Area under ROC curve for TRT was 0.82 (95% CI 0.69-0.96, *p*-value 0.004).

underwent DMSA renal scintigraphy at six months after UTI. Three patients lost to follow-up visit. There were nine girls and eight boys, VUR and no VUR were found in 10 and seven patients, respectively. Fifteen patients developed persistent abnormal DMSA renal scintigraphy. There were eight girls and seven boys, VUR and no VUR were found in 10 and five patients, respectively. From 20 patients, at least 75% of patients who had abnormal DMSA renal scintigraphy at 1-month would have abnormal DMSA renal scintigraphy at six months after UTI.

Discussion

The authors, in previous retrospective study, found no correlation between age groups and sex with DMSA renal scintigraphy results on the right and left kidneys[13]. This result also was confirmed by other studies[14,15]. However, the majority of patients were older than one year old, whereas, the majority of patients in this prospective study were younger than one year old. Zaki et al[16] also reported that girls were more likely to develop acute pyelonephritis and renal scarring than boys. However, Soylu et al[17] showed that male and girls age at or more than 27 months were independent indicators of renal scarring. Ansari et al[6] and Martín Aguado et al[18] found that older age at the time of presentation was the predictor of abnormal DMSA renal scintigraphy. Orellana et al[19] showed that permanent renal damage was more likely in children older than one year and there were no differences in renal damage between boys and girls. Vachvanichsanong et al[4], by multivariate analysis, revealed that age of diagnosis of VUR older than five years and male gender were significant risk factor for renal scarring. However, there were studies that showed no correlation between renal scarring and age at diagnosis[10,20].

The authors showed a mean TDT of two days in both normal and abnormal DMSA renal scintigraphy. Therefore, TDT did not predict abnormal DMSA renal scintigraphy at 1-month after UTI. Other reports also showed that TDT had no correlation with renal scarring[10,12,20,21]. However, Oh et al[7] demonstrated that TDT was longer in patients who had acute abnormal DMSA renal scintigraphy and ultimately scar formation compared with patients who had normal DMSA renal scintigraphy and no scar formation. TDT at or more than 48 hours predicted abnormal DMSA renal scintigraphy in children with first episode of UTI[6,8]. Tappin et al[21] showed that TDT more than five days predicted abnormal DMSA renal scintigraphy in acute phase. Winberg et al[22] reported that when treatment was delayed renal scar developed in 17%, whereas when prompt and adequate treatment was applied, renal scar developed in only 4.5%. Doganis et al[23] reported renal inflammatory change in 41% of children treated within the first 24 hours since onset of fever, but the incidence increased to 59% if treated on the second day of the infection and to 72% when they were treated between days 3 to 8. However, the frequency of renal scarring in infants treated early and in those with delayed treatment did not differ. This suggests that once acute pyelonephritis has occurred, renal scarring is independent of the timing of treatment.

The authors showed mean TRT in normal and abnormal DMSA renal scintigraphy at 14 and 36 hours, respectively at *p*-value 0.001. The shorter mean TRT of normal than abnormal DMSA renal scintigraphy were also confirmed by Gilani et al[6] (23.5 and 47.4 hours, respectively at *p*-value 0.001) and Fernandez-Menéndez et al[8] (15.9 and 29.7 hours, respectively at *p*-value less than 0.001). The area under ROC curve for TRT was 0.76 (95% CI 0.64-0.86) at *p*-value 0.001. The study showed TRT at or more than 22 hours predicted abnormal DMSA renal scintigraphy at 1-month after UTI with sensitivity 80.0% (56.3-94.1) and specificity 63.6% (47.8-77.6). TRT at or more than 24 hours predicted acute phase abnormal DMSA renal scintigraphy in children with first episode of UTI had previously been reported[6,8]. This signifies the important of time factor especially TRT in the development of renal damage. However, other reports

showed that TRT had no correlation with renal scarring[12,20].

The authors further studied the impact of TDT and TRT on DMSA renal scintigraphy in the presence of non-refluxing and refluxing UTI. In no VUR patients, mean TRT in normal and abnormal DMSA renal scintigraphy was 14 and 45 hours, respectively at *p*-value 0.002. The area under ROC curve for TRT was 0.82 (95% CI 0.69-0.96) at *p*-value 0.004. TRT at or more than 25 hours predicted abnormal DMSA renal scintigraphy at 1 month after UTI with sensitivity 88.9% (95% CI 51.7-98.2) and specificity 68.4% (95% CI 51.3- 82.5). TRT in the presence of non-refluxing and refluxing UTI had not been reported in predicting acute renal damage or renal scarring. This result can have a role in clinical practice of UTI in childhood. No VUR patients with first episode of UTI who had TRT at or more than 25 hours should receive DMSA renal scintigraphy. In VUR patients, there were no significant differences in all tested parameters. This could be due to small sample size of VUR patients in our study. Larger scale study should be conducted to verify these results.

Shaikh et al[24] did a systematic review which DMSA renal scintigraphy was performed within 15 days and five to 24 months after diagnosis of the first episode of UTI. The results showed that 57% had change consistent with acute pyelonephritis and 15% had evidence of renal scarring on the follow-up DMSA renal scintigraphy. The majority of acute renal damage resolved during follow-up period. Snodgrass et al[25] obtained DMSA renal scintigraphy at or beyond three months after UTI. Focal DMSA defects were present in 15.5%. In order to save cost of repeated DMSA renal scintigraphy at 6-month after UTI, the authors performed late acute DMSA renal scintigraphy at 1-month after UTI. In the sixty-seven patients, fifteen (22.4%) patients showed persistent abnormal DMSA renal scintigraphy at 6-month after UTI. Only two (11.8%) out of 17 patients had renal damage resolved. The result showed that if renal damage would resolve, the majority of them would happen within the first month after UTI and the minority would happen after more than one month after UTI.

In conclusion, TRT at or more than 22 hours predicts renal damage after the first episode of UTI. In patients with no VUR, TRT at or more than 25 hours predicts renal damage. DMSA renal scintigraphy in the first episode of UTI should be considered in these patients.

What is already known on this topic?

Girls were found to have abnormal DMSA renal scintigraphy than boys. TDT did not predict abnormal DMSA renal scintigraphy. The shorter mean TRT of normal than abnormal DMSA renal scintigraphy was confirmed. This study signified the important of time factor especially TRT in the development of renal damage.

What this study adds?

The authors studied the impact of TDT and TRT on DMSA renal scintigraphy in the presence of non-refluxing and refluxing UTI. No VUR patients with first episode of UTI who have TRT at or more than 25 hours should receive DMSA renal scintigraphy. The result showed that if renal damage would resolve, the majority of them would happen within the first month after UTI and the minority would happen after more than one month after UTI.

Acknowledgement

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Potential conflicts of interest

None.

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เวลาในการตอบสนองต่อการรักษามีผลต่อความเสียหายที่ไตในผู้ป่วยไข้ติดเชื้อทางเดินปัสสาวะครั้งแรก

สุโรจน์ ศุภเวคิน, เสาวลักษณ์ ฮุนนางกูร, นันทิยา ประวิทย์สิทธิกุล, สิวินีย์ คูธนะวนิชพงษ์, สุนันทา เชี่ยววิทย์, นันทวัน ปิยะภาณี, อนิรุธ ภัทราคาญจน์, อัจฉรา สัมบุณณานนท์

วัตถุประสงค์: *เพื่อประเมินความสัมพันธ์ของเวลาที่ล่าช้าในการรักษาและเวลาในการตอบสนองต่อการรักษากับความเสียหายที่ไตในผู้ป่วยไข้ติดเชื้อทางเดินปัสสาวะครั้งแรก*

วัสดุและวิธีการ: *การศึกษาไปข้างหน้าในผู้ป่วยเด็ก 67 ราย ซึ่งได้รับการวินิจฉัยติดเชื้อทางเดินปัสสาวะครั้งแรกที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างปี พ.ศ. 2551 ถึง พ.ศ. 2553 เพื่อประเมินความเสียหายที่ไตมีการตรวจ dimercaptosuccinic acid (DMSA) renal scintigraphy ที่ระยะเวลา 1 และ 6 เดือนภายหลังการติดเชื้อ*

ผลการศึกษา: *พบความผิดปกติด้วยการตรวจ DMSA renal scintigraphy ในผู้ป่วย 20 ราย ร้อยละ 29.9 ความสัมพันธ์ของเวลาที่ล่าช้าในการรักษากับความผิดปกติด้วยการตรวจ DMSA renal scintigraphy ไม่พบว่ามีความแตกต่าง ขณะที่เวลาในการตอบสนองต่อการรักษามีความแตกต่างอย่างมีนัยสำคัญที่ p-value เท่ากับ 0.001 โดยมีพื้นที่ใต้ receiver operating characteristic (ROC) curve สำหรับเวลาในการตอบสนองต่อการรักษาเท่ากับ 0.76 (95% confidence interval (CI) 0.64-0.86) ที่ p-value เท่ากับ 0.001 ค่าจุดตัดที่เหมาะสมสำหรับเวลาในการตอบสนองต่อการรักษาเท่ากับ 22 ชั่วโมง โดยมีค่าความไวที่ร้อยละ 80 (95% CI 56.3-94.1) และค่าความจำเพาะที่ร้อยละ 63.6 (95% CI 47.8-77.6) ในผู้ป่วย 50 ราย ที่ตรวจไม่พบว่ามีปัสสาวะไหลย้อน เวลาในการตอบสนองต่อการรักษามีความแตกต่างอย่างมีนัยสำคัญที่ p-value เท่ากับ 0.002 โดยมีพื้นที่ใต้ ROC curve สำหรับเวลาในการตอบสนองต่อการรักษาเท่ากับ 0.82 (95% CI 0.69-0.96) ที่ p-value เท่ากับ 0.004 ค่าจุดตัดที่เหมาะสมสำหรับเวลาในการตอบสนองต่อการรักษาเท่ากับ 25 ชั่วโมงโดยมีค่าความไวที่ร้อยละ 88.9 (95% CI 51.7-98.2) และค่าความจำเพาะที่ร้อยละ 68.4 (95% CI 51.3-82.5)*

สรุป: *เวลาในการตอบสนองต่อการรักษาที่เท่ากับหรือมากกว่า 22 ชั่วโมง สามารถทำนายความเสียหายที่ไตในผู้ป่วยไข้ติดเชื้อทางเดินปัสสาวะครั้งแรก ในผู้ป่วยที่ตรวจไม่พบว่ามีปัสสาวะไหลย้อนเวลาในการตอบสนองต่อการรักษาที่เท่ากับหรือมากกว่า 25 ชั่วโมง สามารถทำนายความเสียหายที่ไตได้ ผู้ป่วยไข้ติดเชื้อทางเดินปัสสาวะครั้งแรกที่เข้าเกณฑ์ดังกล่าวข้างต้น ควรที่จะได้รับการพิจารณาตรวจ DMSA renal scintigraphy*