J Surg Med. 2020;4(12):1177-1181.
DOI: 10.28982/josam.803699

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

A pediatric nephrologist's experience on real-time ultrasound-guided kidney biopsy

Bir çocuk nefroloğunun eş-zamanlı ultrasonografi eşliğinde böbrek biyopsisi deneyimi

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Abstract

Aim: Kidney biopsy is crucial in management of renal diseases. Biopsies in children have added difficulties. The aim of this study is to investigate our 5-year experience of real-time ultrasound (USG)-guided percutaneous renal biopsy (PRB).

Methods: Institutional database of children who underwent PRB in a tertiary hospital between January 2015 and March 2020 were evaluated retrospectively. A single pediatric nephrologist performed all the biopsies using an automated spring-loaded biopsy gun under real-time USG guidance.

Results: Thirty-two biopsies were performed in 17 males (53.1%) and 15 females (46.9%), and the median age of the children was 14.5 years. The most common indication for biopsy was nephrotic syndrome in 13 /32 children (40.6%). Median number of glomeruli obtained from biopsy specimens was 18 (min-max=7-54 glomeruli). A diagnosis was achieved in all cases (100%) by a histopathologist. The only complication observed in a 16-year-old boy was a self-limited gross hematuria (3.1%) episode with subcapsular hematoma.

Conclusion: Real-time USG-guided PRB with an automated biopsy gun is an effective and safe technique, providing superior yield when performed by a pediatric nephrologist. Performing kidney biopsy is an essential tool in a nephrologist's workshop.

Keywords: Kidney biopsy, Children, Simultaneous ultrasonography, Biopsy gun

Öz

Amaç: Böbrek biyopsisinin böbrek hastalıklarının yönetiminde oldukça önemli bir yeri vardır. Özellikle çocuklarda yapılan biyopsiler ek zorluklar gösterir. Bu çalışmanın amacı, çocuklarda uygulamış olduğumuz beş yıllık ultrasonografi eşliğinde perkutan böbrek biyopsisi (PRB) deneyimimizi değerlendirmektir.

Yöntemler: Ocak 2015- Mart 2020 arasında bir üçüncü basamak hastanesinde PRB uygulanan çocukların hastane kayıtları geriye dönük olarak irdelenmiştir. Tüm biyopsiler, eş zamanlı USG altında tek bir çocuk nefroloğu tarafından otomatik biyopsi tabancası kullanılarak uygulanmıştır.

Bulgular: Medyan yaşı 14,5 yaş olmak üzere; 17 erkek (%53,1) ve 15 kız çocuğuna (%46,9) 32 böbrek biyopsisi uygulandı. En sık biyopsi endikasyonu, çocukların 13/32'sinde (%40,6) nefrotik sendrom idi. Biyopsi örneklerinden alınan medyan glomerül sayısı 18 (min-max=7-54 glomerül) idi. Histopatolog tarafından tüm olgularda (%100) tanı konulabildi. Gözlenen tek komplikasyon, 16 yaşındaki bir erkek çocuğunda subkapsüler hematomla birlikte kendiliğinden düzelen gross hematüri süreci idi (%3,1).

Sonuç: Çocuklarda; PRB Bir çocuk nefroloğu tarafından otomatik biyopsi tabancası kullanılarak, eş-zamanlı USG altında yapıldığında, yeterince fazla örneğin alınmasını sağlayan, etkili ve güvenli bir tekniktir. Böbrek biyopsisi, bir nefroloğun çalışma sorumluluğunda yapması gereken önemli bir uygulamadır.

Anahtar kelimeler: Böbrek biyopsisi, Çocuklar, Eş-zamanlı ultrasonografi, Biyopsi tabancası

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Ethics Committee Approval: The study was approved by the institutional review board. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, kurumsal inceleme kurulu tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

How to cite/Atıf için: Şimşek B. A pediatric nephrologist's experience on real-time ultrasound-guided kidney biopsy. J Surg Med. 2020;4(12):1177-1181.

Introduction

Kidney biopsy is the gold standard in the diagnosis, prognosis and management of many renal diseases [1]. However, there is a downward trend in number of biopsy-performing nephrologists over last years, provoking a novel debate over a nephrologist's job description.

Since Iversen and Brun introduced percutaneous renal biopsy (PRB) in 1951, advances have emerged in biopsy technique from indirect visualization to real-time ultrasound (USG) guidance [2]. Biopsy devices also have been evolved from the introduction of Vim-Silverman needle to spring-loaded automated biopsy gun [2,3]. Today, automated spring loaded biopsy device is being used with real-time USG guidance by many kidney biopsy performers [1]. Despite the advances in safety, handiness, and remarkably improved diagnostic power, with the use of "automated spring-loaded biopsy gun," this invasive procedure is not risk-free, depending partly on the skill of the operator or the clarity of imaging of the needle-tip's path in the USG screen [4,5]. Complications of PRB range from minor perirenal hematomas to major bleedings requiring blood transfusions and rarely up to the loss of kidney [6].

Furthermore, biopsies in children have added difficulties due to smaller kidney size and decreased ability of the patient to co-operate [3]. Additionally, there has been a diversity of implementations in performing kidney biopsy among nephrology clinics. Thus, British Association of Pediatric Nephrology (BAPN) had emphasized the need of a protocol for standardization for renal biopsies in 2003 and revised thereafter in 2010 and 2015, amid optimized protocols for USG-guidance in kidney biopsy in children and guidelines for percutaneous needle biopsy for radiologists were also been proposed [6-9]. However, more has been required to determine optimized global standards for kidney biopsies in children [6].

Although "The Accreditation Council on Graduate Medical Education" requires nephrologists' competence in performing native and allograft PRBs, 15-20% of young nephrologists admitted that they did not feel competent in performing PRBs in a survey between 2004 and 2008 [1,4]. Moreover, many nephrology related skills have been taken over by non-nephrologists in a variety of institutions in recent years, scaling the appeal down of nephrology as a sub-specialty for young doctors.

The aim of this study is to retrospectively investigate the 5-year experience of a pediatric nephrologist on real-time USG-guided PRB using an automated biopsy gun, compare complication rates and diagnostic power of biopsies with the literature, and evaluate the varieties of complications, sample adequacy, biopsy indications and diagnoses made in children.

Materials and methods

Institutional database of 32 children who underwent PRB in a tertiary hospital between January 2015 and March 2020 were evaluated retrospectively. The study was approved by the institutional review board. There was no conflict of interest associated with this study. Signed informed consents from a parent had been obtained before the procedures.

To the best of our knowledge, currently, our 5-year-old unit stands out in performing PRB under real-time USG-guidance with a spring-loaded automated biopsy gun by a pediatric nephrologist, among many pediatric nephrology clinics that perform blind biopsies after USG localization or referring to radiologists for biopsies in Turkey.

Specifically, demographic data (age, gender), clinical symptoms and signs, accompanying clinical diagnoses, laboratory findings including estimated GFR (eGFR) at presentation, indications, and complications of the biopsy with histological diagnoses of children were gathered [1,10-12]. Clinical diagnosis of hypertension was evaluated according to "American Academy of Pediatrics Clinical Practice Guideline" [13].

A pediatric nephrologist confirmed indications and evaluated the contraindications prior to biopsies [1]. "The British Association of Paediatric Nephrology" (BAPN) standards were followed as a standard preparation procedure [7,8]. Vital signs and oxygen saturations of the patients were monitored throughout the procedure [8]. Biopsies were performed in the treatment room on the ward to ease the patient transport to bed. Patients were placed in the prone position with a sandbag set under the abdomen for native kidney biopsies whereas transplanted patients laid supine. Kidneys were scanned with an USG machine (Toshiba Aplio 80 SSA-770A) using a 3.75 MHz transducer by the nephrologist to determine the optimal biopsy site. Lower pole of the left kidney in native or upper pole in the transplant kidney were regarded as the preferred biopsy sites. The area was set; then a small incision was made in the skin following prilocaine administration. Local sterility standards were adhered throughout the procedures. If needed, the child was sedated consciously with midazolam (0.05-0.6 mg/kg body weight) or additionally Ketamine (0.5–2 mg/kg body weight) only after the initial sedation. Biopsy was performed under general anesthesia in patients considered inappropriate for conscious sedation.

A single pediatric nephrologist performed all the biopsies using an automated spring-loaded biopsy gun (Bard Magnum US Patent 5.546.947) loaded with a 16 Gauge needle (16 G tru-cut Gallini BM Italy) under real-time USG guidance. Following infiltration of the anesthetic agent, the biopsy needle was advanced through the incision site with an approximately $30\text{-}40^0$ angle into the skin until the tip was seen pushing on the kidney at USG; subsequently the gun was fired and removed to check for tissue specimen. Two cores are obtained in native kidney biopsies and one core for the renal transplant patient [7,8,14]. The cores were immediately transferred in normal saline in Petri plates to a histopathologist who determined with a dissecting microscope whether enough glomeruli were present to enable a diagnosis to be made and allow proper division for light, immunofluorescence and electron microscopic studies.

An USG imaging was performed to assess post-procedure complications immediately after biopsy and repeated before discharge. Desmopressin acetate was administered in none of the cases. Following the procedure, the child was kept on 6-hour strict bed rest and monitored every 30 min (pulse and blood pressure) for 2 h and then hourly for a further 4 h and 2 hourly till discharge. A complete blood count was checked at 1^{st},

4th, 8th hours following the biopsy. Patients were allowed home after 24 h if they were fully conscious, free of pain, and were able to drink and pass urine without gross hematuria.

Sample size and location

In this study, an adequate biopsy was defined as one in which the pathologist could achieve a confident diagnosis, and generally included >10 glomeruli for native biopsy sampling [4,7,8,15,16]. However, an "adequate" specimen was defined as a biopsy with 10 or more glomeruli and at least two arteries, complying to Banff 97 criteria in a transplant biopsy [14].

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS version 21.0). Descriptive statistics such as percentages and median were calculated. $P<0.05$ was considered of statistical significance.

Results

Throughout the study period, 32 biopsies were performed in 17 boys (53.1%) and 15 girls (46.9%); male to female ratio was 1.3:1. Median age of children included in the study was 14.5 years (min-max ages: 3-17 years). Among these, 5 children (15.6%) were aged ≤10 years, and 27 (84.4%) were aged between 11 and 17 years old. Median of body mass index (BMI) was 22.4 kg/m^2 (min-max=16.4-34.1). Median of hemoglobin (Hgb) was 10.8 gr/dl (min-max=9.3-13.9 gr/dl); median eGFR was 94.7 ml/min/1.73m^2 (min-max=11.1-131.1 ml/min/1.73m^2). Estimated GFR was <60 ml/min/1.73m^2 in 7/32 (21.9%) patients (30). Median s-albumin was 3.5 gr/dl (min-max= 1.6-4.8 gr/dl). Hypertension was diagnosed in 5 children on admission; 1 girl, 4 boys, and all were >10 years old (15.6%) (3/5 children: Stage 1 hypertension; 2/5 children: Stage 2 hypertension).

The clinical characteristics considered as a biopsy indication at the time of the biopsy are illustrated in Table 1. The most common indication for biopsy was nephrotic syndrome (NS) in 13 /32 children (40.6%). Only one female patient with FSGS who turned 10 (1/13 (7.6%)) among 13 children was steroid resistant at the time the decision for biopsy was made.

Table 1: Clinical characteristics at the time of renal biopsy

Clinical Characteristics	Cases total / percentage n=32/(%)
Proteinuria (UP/Cre ≥0.5g/g)[1]	7/(21.9%)
Hematuria[2]	6/(18.8%)
Nephrotic Syndrome[3]	13/(40.6%)
Acute Renal Failure	5/(15.6%)
Rapidly Progressive Glomerulonephritis	1/(3.1%)

[1] UP/Cre ≥0.5g/g or clinician marked proteinuria or nephritic syndrome [10], [2]u-Dipstick≥1 or clinician marked hematuria or nephritic syndrome, [3]UP/Cre>2mg/mg, 1g/m^2/d and s-albumin<35g/L or clinician marked nephrotic syndrome [11]

Local anesthesia, conscious sedation with local anesthesia and general anesthesia were performed in 31/32 (96.9%), 3/32(9.4%), and 1/32 (3.1%) patients respectively.

Median glomeruli number obtained from biopsy specimens was 18 (min-max=7-54 glomeruli). A diagnosis was achieved in all of 32 cases (100%) by a histopathologist, despite 2/32 (6.2%) cases from whom 7 glomeruli were obtained individually.

The distribution of histopathological diagnoses is illustrated in Table 2. Glomerulopathies were identified in most cases 25/32 (78.1%), tubulointerstitial nephritis and normal histology constituted the remaining 7/32 (21.9%) of tissue specimen examinations. The most common diagnoses were focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN) and membranous glomerulonephritis (MG), with 5/32 (15.6%) of cases individually.

Table 2: Histopathological Diagnosis following Renal Biopsy

	Histopathology	n (%)
Glomerulopathy	Minimal Change disease	3 (9.4%)
	Membranous GN	5(15.6%)
	FSGS	5(15.6%)
	Membranoproliferative GN	1(3.1%)
	IgM Nephropathy	1(3.1%)
	IgA Nephropathy	5(15.6%)
	Alport syndrome	2(6.4%)
	Acute T cell rejection	1(3.1%)
	Crescentic GN	1(3.1%)
	Postinfectious GN	1(3.1%)
Miscellaneous	TIN	3 (9.4%)
	Normal histology	3(9.4%)
	Juvenile Nephronophthisis	1(3.1%)
	Total	32 (100%)

During the follow-up on the ward, median Hgb levels obtained from patients at the 1st, 4th and 8th hours were 10.8, 10.4, 10.8 gr/dl respectively, neither a statistically significant Hgb descent nor a major complication requiring blood transfusion was seen ($P>0.05$). The only complication due to the procedure was observed in a 16-year-old boy with an eGFR of 28.6 ml/min/1.73m^2 and Stage 1 hypertension had lost his cooperation at the time the biopsy gun had fired. He suffered from gross hematuria (3.1%) in only one urination episode without Hgb descent. Additionally, a 10 mm subcapsular hematoma was observed on ultrasound scene just after the biopsy resolved spontaneously in a week. All patients were discharged after 24 hours, without readmissions due to complications.

Discussion

Herein, an experience of real-time ultrasound-guided PRB with an automated spring-loaded biopsy gun in children by a pediatric nephrologist is presented with the data regarding indications, safety, and efficiency of kidney biopsy, as well as histopathologic diagnoses achieved. Our unit was established in January 2015, hence the patients included in this study were mostly among new admissions and the figures of kidney biopsies were limited compared to populations reported from some prior clinics [1,6].

A quick glance at the demography of the study sample reveals a slight male predominance (1.3:1) that was comparable to sex-specific differences in prevalence reported previously [17,18]. Lee et al. [17] and Printza et al. [18] stated that around half of children who underwent kidney biopsy in their series were under 11 years of age; however, minority of our cases (15.6%) were under 11. The limited study population or abundance of first admissions might contribute to such a discrepancy.

The major indication for kidney biopsy was NS (40.6%) among the study population, in accordance with the previous reports [1,5,17,18]. Printza et al. reported NS as the main indication (34.5%), whereas Tondel et al. not only pointed out the higher frequency of NS (40.1%), but also represented proteinuria (79.3%) as the primary reason for biopsy in Norwegian children [1,18]. However, hematuria was claimed as a leading indication in some reports [5,17]. Hematuria was the third frequent indication following proteinuria in our study.

There is paucity of data regarding the efficiency of biopsy guns and PRB outcomes in children [3,7,16]. Automated

biopsy gun offers an easier, single-step and faster and effective technique to obtain kidney tissue in children. Because of the speed of cutting and the more tightly packed glomeruli nature of child kidney, a rapid–firing biopsy gun allows superior yield with less tissue damage with even smaller-bore needles [3,7,16]. With real-time USG guidance, the ability to obtain adequate renal tissue for a diagnosis rose >95% of renal biopsies performed by a biopsy gun [4,5]. Whittier et al. reported a perfect diagnostic yield, constituting 92% of 767 native and 885 of 938 renal transplant biopsies including 10 glomeruli or more, with sufficient tissue for making a diagnosis in over 99% of cases [19]. Pongsittisak et al. [20] recently reported superior yield with real-time USG-guided PRB compared to blind PRB. A diagnosis was achieved in all children (100%) included in our study, with a perfect diagnostic yield in 93.8% and a sufficient tissue obtained in 6.2% of biopsies, indicating a higher diagnostic efficiency of the technique.

Kidney biopsy is crucial in the research of renal diseases, changing the initial clinical diagnosis in more than 50% and therapy in 30% of cases [4,5,21]. Glomerulopathies were the major diagnosis (78.1%), enabling proper treatments and managements in our study, compatible with figures of Printza et al. (80%). The frequencies of histopathologic diagnoses in this study were comparable with the literature reporting IgAN as the most prevalent form of GN worldwide [17].

Besides its superior diagnostic competence and safety, PRB guided by real-time USG is not complication free. Among several complications after renal biopsy, macroscopic hematuria and perirenal hematoma are the most common [19,22,23]. However, Tondel et al. reported percentage of gross hematuria in children as 1.7% and stated that frequency of hematoma was higher in children (8.1%) than adults (3.5%, $P<0.001$), becoming more evident with a rate of 18.9%, during the latest years of the study [1]. Significant bleeding and major complication rates were reported as 4-7% on average, up to 25% and 5.9% of biopsies respectively [4,19,24,25]. There have been conflicting reports indicating bleeding complications were observed more often with 14 and 18 gauge needles [1,5,26]. There are also anomalous essays on effects of biopsy technique over complications, giving hassle to interpret among studies [20]. In this study 16-gauge needles were preferred due to smaller sample size with less diagnostic success of 18-G with a spring–loaded automatic gun under real-time USG in all biopsies [26]. Gross hematuria rate (3.1%) in the study population was slightly lower than the average rate of bleeding complications reported [2]. Similarly, our hematoma ratio was 3.1%, far lower than the figures reported [1]. It might be inaccurate to interpret our data confidently due to the limited sample size.

Advancements in biopsy technique might not stave off risk factors provoking adverse outcomes. Lower Hgb levels in patients with acute kidney injury (AKI), eGFR <60ml/min per 1.73 m^2, systolic hypertension, acute renal failure and smaller clinical size (<30 biopsies/yr) were represented among risk factors for major complications of kidney biopsy. It was reported that the more eGFR declined below 60ml/min per 1.73 m^2, the more tendency for a complication rose; even up to 16 fold when compared with cases with an eGFR>60 ml/ min per 1.73m^2 [2,4,22]. However, although median of Hgb was 10.8 gr/dl, and almost one-fifth of the study population had an eGFR<60 ml min per 1.73m^2 and about 15% were hypertensive, no major complication was seen [1]. Only a self-limited minor complication of macroscopic hematuria episode with subcapsular hematoma was observed in a 16-year-old boy with Stage1 hypertension and an eGFR<30 ml min per 1.73m^2 among the study sample, which was comparable with the reported risk factors [4]. However, a transplant kidney biopsy performed in a 16-year-old boy with an eGFR=11.1ml/min per 1.73m^2 was free from complications. Performing a single needle pass might have accounted for, if any correlation had been reported between the number of passes and complications [1,23,27].

In addition, performing the biopsy on ward was convenient as it eased patient transport. Secondly, real-time USG guidance ensured the confidence achieved with continuous visualization of the needle position in the renal parenchyma and finally, automated biopsy gun shortened biopsy time, providing superior tissue specimen. Since over a third of complications might be detected beyond 8h in patients undergoing native biopsy we observed our patients on ward for 24 h [27].

There has been an ongoing debate over whom the biopsy should be performed by: A nephrologist or a radiologist? Korbet considered the development of the PRB among major technical advancements leading to nephrology becoming a sub-specialty. Although a renal biopsy is regarded among essential skills of pediatric nephrology, there has been an alarming decrease in the number of biopsies done by nephrologists lately [1,2]. Tondel et al. [1] stated that only one third of biopsies were was performed by a nephrologist. Performing PRB has been neglected in fellow curriculum in some centers, subjecting young colleagues to quiz their position as a sub-specialist and dissatisfaction with their career choice. However, a nephrologist is principally responsible from the histopathologic diagnoses provided by the biopsy, directly affecting the care provided for patients.

Conclusion

To sum up, this study claims that real-time USG-guided PRB with an automated biopsy gun is a safe, easy, and quick technique, providing superior yield in kidney biopsies in children. In our study population, its efficacy to reach a diagnosis was high and complication rate was lower than previously reported [1,4]. Acknowledging its limited population size, this study is sort of a challenge, aspiring to call attention to the importance of performing nephrology related skills by nephrologists. Nephrologists should consider kidney biopsy among the principal tools in their workshop, deserving to be embraced tightly.

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