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**SVEUČILIŠTE U ZAGREBU
MEDICINSKI FAKULTET**

Bojana Šimunov

**Vrste biopsija bubrega, komplikacije
metode i prikaz vlastitih rezultata**

ZAVRŠNI SPECIJALISTIČKI RAD



Zagreb, 2020.

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Kidney Biopsy Types, Complications and Outcomes- Our Experience

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Abstract

Background: Kidney biopsy is frequently performed in our centre as an outpatient procedure. The aim of this study was to evaluate the safety of biopsy in the outpatient setting.

Methods: We analysed kidney biopsies performed from March 2013 to February 2017. 725 biopsies performed in the outpatient setting were identified: There were 592 transplant and 133 native biopsies including 3 solitary kidney biopsies. All were performed under ultrasound guidance using a 16G or 18G needle, with freehand technique. In all patients with $\text{eGFR} < 30 \text{ ml/min/1.73m}^2$ desmopressin was administered. Patients were observed for 6h before discharge, with a CBC and urine test after 4h. Major complications were haemorrhage requiring therapeutic intervention or transfusion. Minor complications were significant reduction in Hb levels ($>10\%$), without need for transfusion or intervention and macrohaematuria.

Results: There were 506 (69.8%) male patients. Average age was 50.3 ± 12.7 yrs. Indications for native kidney biopsy included nephrotic syndrome (39.8%), nephritic syndrome (42.9%), follow-up biopsy (15.8%), and other (1.5%). There were no major complications. A decline in Hb was observed in 72% of pts. Average Hb decline was 4.2 ± 6.3 g/L. In 10.1% pts there was $>10\%$ reduction in Hb level, with no evident bleeding, including by ultrasonography. In 2.5% of patients macrohaematuria was present. In a multivariate analysis male gender, lower eGFR, higher prebiopsy Hb and native kidney biopsy were predictive for Hb decline. No therapeutic interventions were required.

Conclusion: We found that kidney biopsy performed in an outpatient setting in select patients is only rarely associated with adverse events and is a safe procedure. It remains a possibility in low-risk patients. In other patients it should be done in the hospital setting due to possibly serious complications.

Key words: kidney biopsy, safety, kidney disease, desmopressin,

Abbreviation list

AV fistula = arteriovenous fistula

BW =body weight

PRBC = packed red blood cells

DDAVP = desmopressin

G = gauge

IV = intravenous

AKI = acute kidney injury

CKD = chronic kidney disease

CT = computed tomography

PT = prothrombin time

APTT = activated partial thromboplastin time

BW = body weight

eGFR = estimated glomerular filtration rate

US = ultrasound

CBC = complete blood count

Hb = haemoglobin

Introduction

Kidney biopsy is an essential part in the diagnosis and management of parenchymal renal diseases.(1) Since its introduction in the 1950s (2) it remains the most exact diagnostic method for kidney parenchymal disease. It provides important information, altering treatment in a high percentage of cases (3). The percutaneous kidney biopsy with real time ultrasound guidance is the current standard of care (3–5). Complications include macrohaematuria, haematoma, AV fistula, bleeding or even nephrectomy. A systematic review and meta-analysis of percutaneous kidney biopsies from 1980 to 2011 (which included 34 studies with 9474 biopsies that had met the inclusion criteria) was performed by Corapi *et al.* (6) , the rates of complications in the review were ranging from 3.5% for macrohaematuria (CI 0.3 to 14.5), over PRBC transfusion in 0.9% (CI 0.4 to 1.5) to nephrectomy 0.01%. The rates of complications differ among centres. (7,8). In recent reports using real-time ultrasound guidance, complication associated with excessive bleeding rates are even more infrequent. (6,7,9)

To avoid adverse events, risk assessment remains crucial. In a recent review (6), predictors of PRBC transfusion included the needle gauge (14 vs. 16 or 18), sex (female), serum creatinine ($\geq 180\mu\text{L}$), low haemoglobin prior biopsy ($\leq 120\text{ g/L}$), AKI, high blood pressure, haemostasis abnormalities and anatomical abnormalities – horseshoe kidney, solitary kidney. Similar findings were reported in some other studies (8,10,11). A historical contraindication, solitary kidney is today no longer reported as a contraindication in some centres (12). As mentioned, the haemorrhagic diathesis present in uremic patients with advanced CKD is associated with higher risk for bleeding. Desmopressin (DDAVP) is the most common agent used to treat or prevent bleeding in uremic patients (13,14). DDAVP improves haemostasis by releasing factor VIII: von Willebrand factor multimers from endothelial cells. Desmopressin reverses uremic platelet dysfunction quickly (circa within one hour of IV injection) for a short duration of time (around 24 h) (15).

With a better safety profile and technological development, kidney biopsy is performed in some centres as an outpatient procedure (6,16). The practice differs among centers even within one country as shown in the study by Bolle *et al* (17). In the outpatient setting it is important to know the timing of complications to determine the optimal post-biopsy observation period. In a study from France (18) 100% of complications occurred in outpatients within 8 hours vs. 72% complications in inpatients, and 10% of inpatients had complications >24h hours after biopsy. Historical data, prior to real-time ultrasound guidance, advised for longer observation periods (19).

Another issue in renal biopsy is whether post biopsy imaging should be routine. In a recent review the utility of post-biopsy ultrasonography or CT has not been shown (3) . A presence of haematoma on post biopsy imaging does not predict clinically relevant complications, but the absence of haematoma has a high negative predictive value and imaging is proposed only when clinically needed (3,20,21).

In our centre biopsy is frequently performed as an outpatient procedure in suitable patients. We performed a retrospective observational study to evaluate the safety of biopsy in the outpatient setting.

Materials and Methods

We analysed native and transplant kidney biopsies performed at University Hospital Merkur outpatient clinic from March 2013 to February 2017. 725 biopsies performed in the outpatient setting were identified. There were 592 biopsies in transplant patients, and 133 native kidney biopsies, including 3 solitary kidney biopsies. On the day of the biopsy complete blood count, international normalized ratio/prothrombin time, activated partial thromboplastin time, serum creatinine, potassium and sodium were obtained. All medications which could increase bleeding risk (e.g. anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory drugs) were omitted for an appropriate period prior to biopsy. Polycystic kidney disease, and radiological evidence of small atrophic kidneys were considered contraindications for biopsy. Abnormalities in haemostasis (prolonged PT, APTT, low platelet count) were contraindications for the procedure in the outpatient setting. Kidney function was determined using the 4-variable Modification of Diet in Renal Disease study equation to estimate glomerular filtration rate (22). In all patients with $eGFR < 30\text{--}45\text{ ml/min/1.73m}^2$ desmopressin ($0.4\text{ }\mu\text{g/kg BW IV}$) was administered prior to the procedure. All biopsies were performed under US guidance using a 16G or 18G automated, spring-loaded needle with freehand technique. Bed rest for 4 hours was prescribed to all patients. While on bed rest, a 2-kilo sandbag was placed over (in kidney transplant patients) or under (native kidney) the biopsy site. Patients were observed for 6 h before discharge. A CBC and a urine test were performed after 4 hours. Ultrasonography was performed upon attending clinician discretion. All patients were told to visit the emergency room if they developed any symptoms including pain, increasing heart rate, dizziness, or fever after discharge. Study outcomes were major and minor complications. Major complications were defined as haemorrhage requiring therapeutic intervention to stop bleeding and/or packed red blood cell (PRBC) transfusion. Minor complications were defined as significant reduction in Hb levels ($>10\%$), without need for PRBC

transfusion and/or intervention to stop bleeding and macrohaematuria, without intervention to stop bleeding.

Statistical analysis

Statistical analysis was performed using Statistica v13.1 (Dell Software Inc, San Francisco, USA). P value <0.05 was considered significant. The data are expressed as the median and range, or mean with standard deviation, as appropriate. Categorical variables are presented as frequency counts and percentages. The categorical values were compared using χ^2 test and continuous values between the two groups were compared using Student's t-test, or Mann-Whitney test in case of not-normally distributed values. Correlations between the two continuous variables were tested by the Pearson correlation. A multiple regression analysis was performed to assess independent predictors of Hb decline. We included into multivariate analysis all variables that were associated with Hb decline in univariate analysis with $p \leq 0.1$.

Results

There were 219 (30.2%) female and 506 (69.8%) male patients. Average age was 50.3 ± 12.7 yrs. Indications for native kidney biopsy included nephrotic syndrome (39.8%), nephritic syndrome (42.9%), follow-up biopsy (15.8%), and other (1.5%). From 592 transplant biopsies 72.8% were indication and 27.2% were protocol biopsies. The study population characteristics can be seen in Table 1. The glomerular yield in 97.5% of biopsies was sufficient for analysis. A decrease in haemoglobin was observed in 72% of patients. Average haemoglobin decline postbiopsy was 4.2 ± 6.3 g/L ($3.4\% \pm 5.2\%$) (Table 1). There were no major complications requiring an intervention to stop bleeding, or blood transfusion (Table 2). In 10.1% of patients there was >10% reduction in Hb level, with no evident bleeding, including by US. In 2.5% of the patients postbiopsy macrohaematuria was present, without requirement for intervention or blood transfusion. In 61.9% of patients the decrease in haemoglobin was less than 10%. In 28% of patients there was no haemoglobin decline after biopsy. Microhaematuria was present in 78.6% of patients. 11 patients (1.5%) were hospitalized for overnight monitoring; all were discharged the next day. There were no therapeutic interventions required for biopsy complications. All patients included in the study had multiple follow-up visits so we can be sure that there were no late complications.

The subgroup analysis between patients with native kidneys and transplanted is shown in the Table 3. Haemoglobin prior to biopsy, eGFR and the decline in haemoglobin were higher in the native kidney group ($p=0.02$, $p<0.001$ and $p=0.04$ respectively).

In univariate analysis age, eGFR, needle gauge and the number of passes were not predictive for post biopsy haemoglobin decline. Prebiopsy Hb ($p=0.037$), male sex ($p=0.002$) and native vs. transplant kidney biopsy ($p=0.04$) were predictive of decline (Table 4). The multivariate analysis is shown in Table 5.

Table 1 Study population characteristics (n=725)	
Native kidney; n (%)	133 (18.4)
Transplanted kidney; n (%)	592 (81.6)
surveillance	161 (27.8)
indication	431 (72.8)
Female; n (%)	219 (30.2)
Age (years)	50.3 ±12.7
Mean serum creatinine, µmol/L	150.3±67.8 (range 36 to 678)
eGFR, ml/min/1.73m ²	51.3±24.4
Desmopressin	82 (11.3)
Needle gauge	
16	18 (2.5)
18	642 (88.6)
N/A	65 (8.9)
Number of passes (n=652)	2.1±0.7(range 1 to 7)
Hb prebiopsy, g/L	124.4±19.8 (range 71 to 181)
Hb postbiopsy, g/L	120.3±20.3 (range 71 to 186)
Average Hb decline, g/L (%)	4.2±6.3 (3.4 ± 5.2)
Data are presented as number (percentage), mean ± standard deviation, range. Haemoglobin (Hb), estimated glomerular filtration rate (eGFR).	

Table 2 Biopsy related complications (n=725)	
Macrohaematuria	18 (2.5)
Reduction in Hb >10%	73 (10.1)
Local haemorrhage	1 (0.1)
Interventions	0 (0)
Hospitalization	11 (1.5)
Data are presented as number (percentage).	

Table 3 Transplant vs native biopsies			
	Transplant (n=592)	Native (n=133)	p
Age, yrs	50.6 ±12.1	49.3±15.2	0.31
Male; n (%)	421(71%)	85(64%)	0.2
Hb prebiopsy, g/L	123.6±19.5	127.9±20.9	0.02
Hb postbiopsy, g/L	119.7±20.0	122.8±21.7	0.11
ΔHb, g/L	3.9±6.3	5.2±6.4	0.04
Hb postbiopsy/ Hb prebiopsy	0.97±0.05	0.96±0.05	0.05
eGFR, mL/min/1.73m ²	49.3±19.7	60.1±37.8	<0.001
Data are presented as number (percentage), mean ± standard deviation. Haemoglobin (Hb), estimated glomerular filtration rate (eGFR).			

Table 4 Univariate analysis of Hb decline predictors		
	Mean ± SD	p
Sex (male vs. female)	4.67 ±6.16 vs. 3.06 ±6.62	0.002
Transplant vs. native	3.94 ±6.29 vs. 5.21 ±6.42	0.04
	R	
Age (per year)	0.062	0.098
eGFR (per ml/min/1.73 m ²)	-0.064	0.087
Hb prebiopsy (per g/L)	0.078	0.037
No of passes	-0.072	0.066
Haemoglobin (Hb), estimated glomerular filtration rate (eGFR). Standard deviation (SD)		

Table 5 Multivariate analysis of Hb decline predictors				
	delta Hb p	delta Hb Beta (β)	-95.00% Cnf.Lmt	+95.00% Cnf.Lmt
Age (per year)	0.162	0.059	-0.024	0.142
Hb prebiopsy (per g/L)	0.012	0.109	0.024	0.194
eGFR (per ml/min/1.73 m ²)	0.043	-0.091	-0.179	-0.003
Number of passes	0.027	-0.087	-0.164	-0.010
Sex (M)	0.039	0.084	0.004	0.164
Type (transplant)	0.002	-0.124	-0.201	-0.046
Haemoglobin (Hb), estimated glomerular filtration rate (eGFR), male sex (M).				

Discussion

We analysed the safety of outpatient native and transplant kidney biopsies in a large tertiary renal centre. University Hospital Merkur has the largest kidney biopsy volume in Croatia. In our outpatient biopsy cohort, no severe complications leading to an intervention, or to kidney loss were recorded during the period analysed. Complications that occurred were due to bleeding, similar as in other larger studies (23,24). The paucity of complications in the study can be partially explained by a large proportion (81,6%) of transplanted kidney biopsy in our cohort, as evidenced from the Table 5. The anatomical localisation of the transplanted kidney makes them easier to visualise and to biopsy.

A similar study of kidney allograft biopsies (25), showed a rate of complications of 1.8%, mostly comprising of mild complications (0.7%) and only 0.19% life-threatening complications. The difference in the study was that it comprised all allograft biopsies from the institution including inpatient biopsies and early post-transplant biopsies, although the majority were in outpatient biopsies. A favourable safety profile for outpatient kidney allograft biopsies was also reported from a paediatric study (26), with an incidence of adverse events 9.2%. A large majority of those were micro- and macroscopic haematuria (8.4%).

Our results are similar, with 2.5% complication rate for macroscopic haematuria, without the need for intervention. 10.1% experienced a decline in postbiopsy haemoglobin larger than 10%, but also without the need for PRBC transfusion. Only one patient had prolonged local bleeding which resolved spontaneously.

All patients with eGFR of less than 30-45 ml/min/1.73 m² received desmopressin to prevent bleeding, according to current recommendations in uremic patients (13,14). We also employed strict control of coagulation parameters and omitting of antiplatelet or anticoagulant agents for several days prior to biopsy. This is different from some other centres policies, where routine antiplatelet agent pause had not been routinely advocated (27). A possible reason of a low incidence of complications overall may be the use of

16G and 18G (in a majority of our patients), instead of 14G needles, as described in other studies, thus minimising the bleeding risk (6,8,28,29).

Our results show that outpatient biopsy, as performed in our centre is a safe procedure. Crucial to a good safety profile may be large centre volume, careful risk assessment prior to biopsy and the selection of lower risk patients for outpatient biopsy.

Our study has limitations. This is a retrospective, single centre study. However, patient data and biopsy complications were prospectively recorded, minimising underreporting of complications. Nevertheless, for a definite conclusion about safety of outpatient kidney biopsy, a larger sample size and a multi-centre prospective study would be necessary.

We found that kidney biopsy performed in an outpatient setting in select patients is only rarely associated with adverse events and is a safe procedure. It remains a possibility in low-risk patients. In other patients, kidney biopsy should be done in the hospital setting due to possibly serious complications.

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Conflict of Interest Statement

The authors have no conflicts to declare. The results presented in this paper have not been published previously in whole or in part, except in abstract format.

Authors' Contributions

BS designed the study, collected and analysed the data and wrote the manuscript. MG and BC participated in designing the study and critically reviewed the manuscript. MK supervised the design of the study, supervised collection of data and analysis, and participated in writing the manuscript.

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Statement of Ethics

The subjects gave their informed written consent for the procedure and for the collection of data for research purposes. The present study results reflect retrospective evaluation of standard of care practice at our centre so no ethics committee approval was required.

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Životopis

Bojana Šimunov (r. Gardijan), rođena je 22. listopada 1987. u Zagrebu. Nakon završene V. gimnazije upisala je Medicinski fakultet Sveučilišta u Zagrebu 2006. godine. Diplomirala je 2012. Tijekom studija dobila je Dekanovu nagradu i Nagradu Zaklade Krmpotić-Perović za najbolju studenticu generacije. Nakon odrađenog pripravničkog staža u Kliničkom bolničkom centru Zagreb položila je stručni ispit i stekla odobrenje za samostalni rad 2013.godine. Od 2014. zaposlena je kao specijalizant nefrologije pri Zavodu za nefrologiju Klinike za unutarnje bolesti Kliničke bolnice Merkur. Tijekom specijalizacije usavršavala se i u Universitaets Klinikum Eppendorf, Hamburg. Od 2015. vanjski suradnik Medicinskog fakulteta u Zagrebu na predmetu Temelji liječničkog umijeća. Član je Hrvatskog društva za nefrologiju, dijalizu i transplantaciju Hrvatskog liječničkog zbora, European Renal Association-European Dialysis and Transplant Association i American Society of Nephrology. Autor više znanstvenih i stručnih publikacija. Udana, majka dvoje djece.