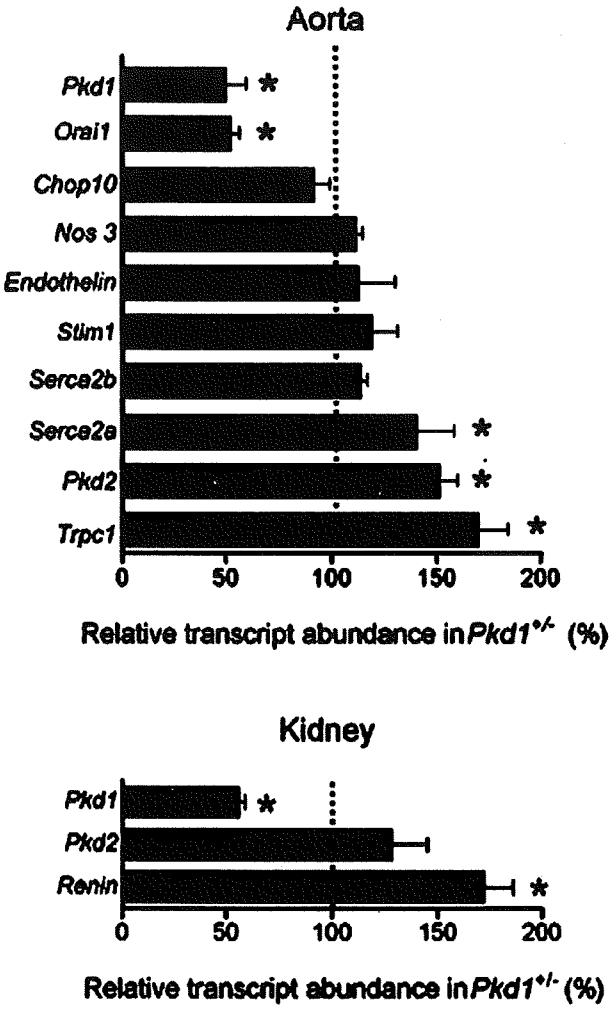

Fig. 5 Real-time q-PCR quantification of the mRNA expression of mediators involved in the vascular reactivity in the aorta of *Pkd1* mice. The mRNA levels (mean±SEM) were first adjusted to *Gapdh*, then normalized to the WT level (set at 100%) using the Pfaffl formula [29]. Nine pairs of aortas and four corresponding pairs of kidneys were analyzed. *$P<0.05$ vs. WT expression level set as 100%

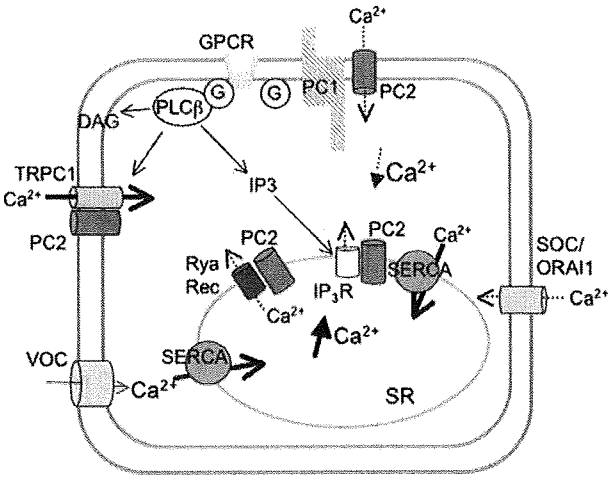

Fig. 6 VSMC phenotypic alterations associated with *Pkd1* deficiency. In $Pkd1^{+/-}$ vascular smooth muscle cell, decrease in *Pkd1* together with an increase in *Serca2a* and in *Pkd2* expression is associated with decrease in cytosolic Ca^{2+} concentration and increase in SR Ca^{2+} content. Increased Ca^{2+} pumping by the SR and inhibition of ryanodine channel following increased expression of *Pkd2* decrease the Ca^{2+} signal evoked by KCl-depolarization. The lower cytosolic Ca^{2+} inhibits IP_3-mediated phenylephrine-evoked Ca^{2+} release. Increased expression of *Pkd2* and *Trpc1* maintains the Ca^{2+} entry component of the Ca^{2+} signal evoked by phenylephrine unaffected. *Dotted lines* indicate inhibition; *bold solid lines* indicate increase of the activities. *PC1* polycystin1, *PC2* polycystin2, *SERCA* sarcoendoplasmic reticulum Ca^{2+} ATPase, *SOC* store-operated channel, *VOC* voltage-dependent Ca^{2+} channel, *IP_3Rec* IP_3 receptor, *RyaRec* ryanodine receptor, *GPCR* G protein-coupled receptor, *G* trimeric G protein, *PLCβ* phospholipase Cβ

CA2a in rat carotid artery results in lower cytosolic Ca^{2+} and higher SR Ca^{2+} content, producing larger BHQ-evoked Ca^{2+} release [20]. Moreover, rapid refilling of the SR by the SERCA pump might decrease the stimulation for capacitative Ca^{2+} entry, as suggested by the smaller Ca^{2+} entry produced by caffeine-evoked Ca^{2+} store depletion in $Pkd1^{+/-}$ vs. $Pkd1^{+/+}$, while the difference was not observed when the Ca^{2+} pump was inhibited by thapsigargin. Furthermore, the increased expression of SERCA2a might also contribute to lower resting cytosolic Ca^{2+} and KCl-evoked global Ca^{2+} signal in $Pkd1^{+/-}$ aortas (Fig. 6). In addition, decreased expression of *Orai1*, which has been shown to form store-operated channel in several cell types and recently in airway smooth muscle cells [26], could prevent proper function of capacitative Ca^{2+} entry.

Part of the Ca^{2+} signal evoked by phenylephrine is caused by Ca^{2+} entry through sarcolemmal voltage-dependent Ca^{2+} channels and nonselective cation channels, identified as members of the TRPC superfamily [2, 13]. The similar Ca^{2+} response evoked by phenylephrine after the addition of Ca^{2+} into the perfusion in $Pkd1^{+/+}$ and $Pkd1^{+/-}$ aortas suggests that the reduced PC1 dosage does not affect the Ca^{2+} entry activated by the α-adrenergic receptor. However, q-PCR analyses showed increased expression of *Pkd2* and *Trpc1* mRNA in $Pkd1^{+/-}$ aortas. TRPC1 is a receptor and a store-operated Ca^{2+} channel [4, 35] that directly associates with PC2 to form heteromeric functional channels [39]. The increased expression of PC2 and TRPC1 in $Pkd1^{+/-}$ aorta might thus constitute a compensatory mechanism allowing the effective activation of Ca^{2+} entry by phenylephrine despite reduced PC1 (Fig. 6).

The present results indicate that Ca^{2+} signaling is dysregulated in the VSMC from $Pkd1^{+/-}$ aorta. An important observation is that the ratio of contraction to cytosolic Ca^{2+} is larger in $Pkd1^{+/-}$ vs. $Pkd1^{+/+}$ aorta. This

observation was confirmed in permeabilized aorta, under condition of controlled cytosolic Ca^{2+} concentration, and in KCl-depolarized artery. Interestingly, the affinity of the contractile machinery for Ca^{2+} was not affected, as indicated by the same pCa value for half-maximal contraction. In the absence of vascular hypertrophy, the origin of this increased contractility is unknown but might be related to a change in the expression of proteins associated with the contractile machinery or to structural alteration in the artery wall. An exaggerated contractile response to phenylephrine associated with a lesser cytosolic Ca^{2+} rise was described in *Pkd2*$^{+/-}$ arteries and attributed to an enhanced Ca^{2+}-independent contraction [32]. The q-PCR studies showed higher *renin* mRNA expression in *Pkd1*$^{+/-}$ kidneys. In rat treated with the Ca^{2+} channel blocker amlodipine, a model also characterized by lower cytosolic Ca^{2+}, increased kidney renin expression is associated with an increase in vascular reactivity to noradrenaline [18]. Further experiments should determine whether subthreshold concentration of angiotensin II, which might be released following enhanced renin expression, might exert sensitizing effect on contractile responses [11].

Hypertension occurs in more than half of ADPKD patients before renal function has become impaired [5]. Using tail-cuff plethysmography, mild hypertension was detected in *Pkd1*$^{+/-}$ mice aged 30 weeks. Increased SBP measured by the same method has been reported in 20-week-old Han/SPRD rats [14]. The hands-off measurement of blood pressure using telemetry revealed that, in stress-free animals, blood pressure was similar in *Pkd1*$^{+/+}$ and *Pkd1*$^{+/-}$ mice. The apparent discrepancy in blood pressure values obtained in conscious mice by the tail-cuff method and by telemetry suggests that 30-week-old *Pkd1*$^{+/-}$ could be more susceptible to the stress associated with handling and restraining conditions [19]. Combined with our findings of enhanced contractile force development in response to alpha-adrenergic stimulation in isolated vessels from *Pkd1*$^{+/-}$ ex vivo, it is very likely that the higher blood pressure values obtained by tail-cuff measurements reflect the higher sensitivity of the vasculature of *Pkd1*$^{+/-}$ animals to the vasoconstrictive effect of endogenous noradrenaline released under stress.

In conclusion, the present data, the first to document a vascular phenotype in heterozygous *Pkd1* mice, indicate that haploinsufficiency in *Pkd1* is associated with a lower cytosolic Ca^{2+} and alterations in Ca^{2+} signaling that are consistent with compensatory changes in the expression of *Pkd2*, *Trpc1*, *Orai1*, and *Serca2a* (Fig. 6). Furthermore, the *Pkd1*$^{+/-}$ aortas exhibit increased contractile responses related to a higher contraction to cytosolic Ca^{2+} concentration ratio. These data emphasize the importance of abnormal Ca^{2+} signaling in ADPKD and give insights into the role of the PC1–PC2 complex in large vessels and the pathophysiology of vascular damage in ADPKD.

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ORIGINAL ARTICLE

Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy

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Abstract
Background Tonsillectomy and steroid pulse (TSP) therapy was proposed as a curative treatment for IgA nephropathy by Hotta et al. (Am J Kidney Dis 38:736–742, 2001) based on data that about 50% of patients achieved clinical remission (CR) of urinary abnormalities.

Materials and methods As a primary survey, we sent a questionnaire and letter to 848 hospitals in Japan, each of which employed a Fellow of the Japanese Society of Nephrology between October and December of 2006, in order to gather information about the prevalence and efficacy of TSP therapy for patients with IgA nephropathy. As a secondary survey, we collected data from both low- and

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high-CR-rate groups to determine which factors predicted resistance to TSP therapy.

Results A total of 2,746 patients received TSP therapy between 2000 and 2006. The CR rates, calculated by measuring urinary criteria 6 and 12 months after TSP therapy, were 32.0% (347/1,085) and 45.6% (452/991), respectively. Analysis of the 30 hospitals in which TSP therapy had been performed on at least ten patients revealed that the CR rates varied from below 10% to 100%. A secondary survey of ten hospitals revealed that, after correction of the CR rate from each hospital, patients could be categorized into three groups: those with a low CR rate (122 patients in four hospitals), a middle CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals). The CR rate of all patients ($N = 303$) was 54.1%. A comparison of patient data between the low- and high-CR-rate groups showed a significant difference in age at onset (years; $P = 0.05$), amount of proteinuria (g/day; $P = 0.02$), total protein (g/dl; $P = 0.02$), pathological grade ($P = 0.009$), and prognostic score as described by Wakai et al. [Nephrol Dial Transplant 21:2800–2808, 2006, ($P = 0.04$)]. Univariate analysis revealed that there was a significant difference between non-CR and CR subgroups in duration from diagnosis until TSP therapy (6.9 ± 6.8 versus 5.3 ± 5.2 years; $P = 0.02$), amount of proteinuria (1.5 ± 1.6 versus 0.8 ± 0.8 g/day; $P < 0.0001$), serum creatinine (0.99 ± 0.40 versus 0.87 ± 0.34 mg/dl; $P = 0.006$), pathological grade ($P = 0.0006$), and Wakai et al.'s prognostic score (37.4 ± 17.8 versus 28.1 ± 15.1; $P < 0.0001$). A multivariate logistic analysis demonstrated that resistance to TSP therapy depends on age at onset, amount of proteinuria, hematuria grade, and pathological grade, and a score predicting resistance to TSP therapy could be derived by the formula: [(−0.0330) × (age) + (0.4772) × log (amount of proteinuria) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894]. A receiver operating characteristic (ROC) curve showed that patients with a resistance score of greater than −0.02 easily resist TSP therapy (sensitivity 69%, specificity 75%, positive likelihood ratio 2.76).

Conclusion TSP therapy shows promise as a treatment that can bring about CR of urinary abnormalities, but unfortunately the average CR rate is about 50% at 1 year after treatment. Predictive factors for resistance to TSP therapy are age at onset, amount of proteinuria, hematuria grade, and pathological grade. The present study suggests that patients with either early-stage or mild to moderate IgA nephropathy easily achieve CR following TSP therapy, whereas patients with late-stage or severe disease are prone to TSP therapy resistance.

Keywords IgA nephropathy · Tonsillectomy · Steroid pulse therapy · Resistance to tonsillectomy and steroid pulse therapy

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Introduction

IgA nephropathy is the most common type of glomerulonephritis in the world, and is characterized by mesangial proliferation with predominantly IgA deposition. A study of patient prognosis showed that, 20 years after disease onset, about 30% of patients had undergone spontaneous remission with a normalized urinalysis and stable kidney function, about 30% had retained stable kidney function but persistent urinary abnormalities, and almost 40% had experienced a progressive course that necessitated dialysis. On the other hand, renal survival rate 20 years after diagnosis is about 60% [1, 2].

Steroid pulse therapy using intravenous administration of 1,000 mg/day prednisolone has been reported to be efficacious at preventing disease progression, with 98% of steroid pulse therapy patients remaining stable 10 years after diagnosis as compared with 65% of placebo-treated patients [3].

There are controversial results about the efficacy of tonsillectomy alone for IgA nephropathy patients. Rasche et al. [4] reported that the renal survival rate of a tonsillectomy group was almost 60% that of a control group at 10 years. On the other hand, Xie et al. [5] demonstrated that the renal survival rate of a tonsillectomy group 20 years after diagnosis was 89.6% compared with 63.7% in a control group, even though there was no significant difference between groups at 10 years.

A retrospective study by Hotta et al. [6] revealed that tonsillectomy and steroid pulse (TSP) therapy induced clinical remission (CR), or absence of urinary abnormalities, in 48% of patients after an observation period of 82.3 ± 38.2 months. Furthermore, the renal survival rate of patients who achieved CR was 100% at 10 years, compared with 77.4% of the group who did not achieve CR.

Following the publication of the above results in 2001, TSP therapy began to be widely used in Japan before a consensus had been reached. The purpose of this study is to determine the prevalence of TSP therapy for patients with IgA nephropathy in Japan, and to identify the factors that predict resistance to TSP therapy 1 year after treatment.

Methods

Primary survey about prevalence of TSP therapy

We sent a questionnaire about TSP therapy for IgA nephropathy patients to 848 Fellows of the Japanese Society of Nephrology. The recipients of the survey worked in hospitals, excluding outpatient and dialysis clinics, between October 27 and December 28, 2006. The questionnaire included the items listed below.

Q1 Have you ever treated IgA nephropathy patients with tonsillectomy and steroid pulse (TSP) therapy? Please continue if you answered "yes."

Q2 When did you start TSP therapy for IgA nephropathy patients?

Before 2000, how many cases did you have?
In 2000, how many cases did you have?
In 2001, how many cases did you have?
In 2002, how many cases did you have?
In 2003, how many cases did you have?
In 2004, how many cases did you have?
In 2005, how many cases did you have?
In 2006, how many cases did you have?

Q3 How many of the patients who received TSP therapy achieved CR within 6 months of starting treatment?

Q4 How many of the patients who received TSP therapy achieved CR within 12 months of starting treatment?

If you answered "no" in Q1

Q4 Are you currently planning to begin TSP therapy for patients with IgA nephropathy?

CR criteria were determined by urinary analysis.

Remission of proteinuria was defined as negative (−) or trace (±) protein on urine dipstick, while remission of occult hematuria was specified as absence of blood on dipstick and urinalysis. CR was defined as complete resolution of both proteinuria and hematuria.

Secondary survey of hospitals in which more than ten patients with IgA nephropathy received TSP therapy

We collected clinical and laboratory data from ten hospitals whose CR rate was over 70% or below 30%, in order to clarify the predictive factors for resistance to TSP therapy. This data included patient age, sex, duration from diagnosis to TSP therapy, grade of proteinuria on dipstick, amount of proteinuria, hematuria grade on dipstick, systolic blood pressure, diastolic blood pressure, serum creatinine, serum total protein, pathological activity score, and prognostic score as outlined by Wakai et al. [7]. We also collected information about the individuals who performed the tonsillectomies and about the steroid amount and pulse timing used in TSP therapy.

Statistical analysis

1. Numerical data are expressed as mean ± standard deviation (SD) and categorical data are reported as proportions. The baseline characteristics of the two patient groups, including age, amount of proteinuria, systolic and diastolic blood pressures, serum creatinine, total protein, and prognostic score [7], were compared using Student's t test, while Fisher's test was used to assess sex, and Mann–Whitney's U test was used to assess urinary occult blood reaction and pathological grade. All P values were two-sided, with $P < 0.05$ indicating statistical significance.
2. A stepwise logistic regression model was performed using each of the predictor variables. All analyses were performed with SAS® software version 9.1 (SAS Institute, Inc., Cary, NC, USA). A receiver operating characteristic (ROC) curve analysis was used to determine the cutoff point on the items which showed significant difference.

Results

Prevalence of TSP therapy in Japan

Of the 848 fellows queried, 317 replied on behalf of the hospitals at which they worked. Despite the response rate of 37.4%, we believe that the present data provides a solid foundation for conclusions about TSP therapy use nationwide because responding hospitals provided the primary source of kidney disease care in their local communities.

1. The number of hospitals performing TSP therapy

Of the 317 responding hospitals, 128 (40.4%) performed TSP therapy for patients with IgA nephropathy.

2. The number of patients receiving TSP therapy in Japan

In 2000 and 2001, an annual total of 140 and 160 patients received TSP therapy, respectively, which included 100 patients per year at Sendai Shakaihoken Hospital. After 2002, the total number of patients treated annually with this modality increased gradually to 220 in 2002, 340 in 2003, 520 in 2004, 690 in 2005, and 620 in 2006. The total number of patients who received TSP therapy between 2000 and 2006 reached 2,746 (Fig. 1).

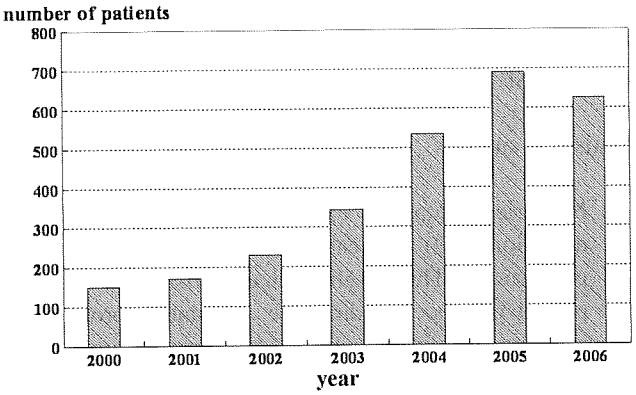

Fig. 1 Prevalence of TSP therapy in Japan. More than 600 IgA nephropathy patients per year received TSP therapy in 2005 and 2006. The total number of patients who have received TSP therapy since 2000 has now reached 2,746

Table 1 CR rate of tonsillectomy and steroid pulse therapy in patients with IgA nephropathy

Months after tonsillectomy	Patient number	Patients in clinical remission	Clinical remission rate (%)
6	1085	347	32.0
12	991	452	45.6

CR rate 1 year after TSP therapy

Of the 2,746 patients who received TSP therapy between 200 and 2006, 1,081 and 991 were evaluated for CR by urinary criteria at 6 and 12 months after TSP therapy, respectively. To eliminate any bias, this analysis excluded the 100 patients per year who received TSP therapy at Sendai Shakaihoken Hospital. The CR rates at 6 and 12 months were 32% (347/1,085) and 45.6% (452/991), respectively (Table 1).

Distribution of CR rate at the 30 hospitals performing TSP therapy on more than ten patients

Figure 2 demonstrates that the CR rate varied from less than 10% to greater than 90% at different hospitals. The high-CR-rate group (greater than 70% CR) consisted of six hospitals, the average-CR-rate group (31–60% CR rate) consisted of 16 hospitals, and the low-CR-rate group (below 30% CR) consisted of 8 hospitals.

Secondary survey

We collected patient data from ten hospitals at which the CR rate was over 70% or below 30%, although the CR rates in four out of the ten hospitals increased or decreased to between 50% and 70% after the addition of new patients.

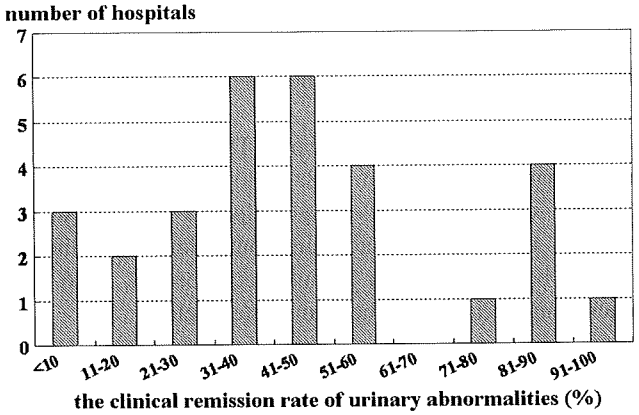

Fig. 2 The distribution of the CR rate at the 30 hospitals performing TSP therapy on more than ten patients. The *X*-axis defines the CR rate (%) and the *Y*-axis indicates the number of hospitals

We divided the ten hospitals into three groups, those with a low CR rate (122 patients in four hospitals), a moderate CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals).

Detailed information about tonsillectomy surgeons and intravenous steroid amount and administration times

There was no difference in surgeons between the low-CR-rate and high-CR-rate groups, because both groups included physicians whose experience levels varied from younger doctors in their third postgraduate year to oto-laryngology specialists who had performed over 200 tonsillectomies each. There was also no significant difference in the amount of intravenous methylprednisolone administered, as all hospitals used 500 mg/day for 3 days as described in Hotta's original report [6]. In the low-CR-rate group, one hospital administered one course of steroids and three hospitals dispensed three courses, while in the high-CR-rate group two hospitals administered three courses. Thus, we found no significant difference between groups in either the surgeons who performed the tonsillectomies nor in the steroid pulse therapy protocols.

Comparison of patient data between low- and high-CR-rate groups

A comparison of patient data between the low- and high-CR-rate groups showed a significant difference in age at onset (30.3 ± 11.1 versus 33.5 ± 13.7 years; $P = 0.05$), amount of proteinuria (1.3 ± 1.4 versus 0.9 ± 0.7 g/day; $P = 0.02$), total protein (6.7 ± 0.6 versus 6.5 ± 0.6 g/dl; $P = 0.02$), pathological grade ($P = 0.009$), and prognostic score as described by Wakai et al. [7] (34.5 ± 15.9 versus 28.8 ± 21.3; $P = 0.04$) (Table 2).

Table 2 Patient profile among the low-, middle-, and high-CR-rate groups and a comparison of patient data between the low- and high-CR-rate groups

	Low-CR-rate group CR rate 30.3%	Middle-CR-rate group CR rate 57.7%	High-CR-rate group CR rate 79.6%	*P*
Number of patients	122	78	103	
Male/female	52/70	41/37	37/66	n.s.
Age (years)	30.3 ± 11.1	40.6 ± 15.1	33.5 ± 13.7	0.05
Years until TSP therapy	7.2 ± 6.2	4.4 ± 5.2	5.9 ± 5.6	n.s.
Proteinuria (g/day)	1.3 ± 1.4	1.2 ± 1.6	0.9 ± 0.7	0.02
Hematuria (0: 1+: 2+: 3+)	7:12:30:73	4:10:25:39	4:25:20:54	n.s.
Systolic BP (mm Hg)	118 ± 16	123 ± 14	121 ± 15	n.s.
Diastolic BP (mm Hg)	73 ± 14	75 ± 11	72 ± 11	n.s.
Cr (mg/dl)	0.94 ± 0.36	0.91 ± 0.27	0.93 ± 0.44	n.s.
TP (g/dl)	6.7 ± 0.6	6.7 ± 0.5	6.5 ± 0.6	0.02
Pathological grade (I: II: III: IV)	6:14:47:55	2:15:40:21	4:32:41:26	0.009
Prognostic score by Wakai et al. [7]	34.5 ± 15.9	32.6 ± 14.1	28.8 ± 21.3	0.04

Table 3 Comparison of non-CR and CR subgroup patient data in all patients who received TSP therapy

	All patients		*P*
	CR rate 54.1%		
	Non-CR	CR	
Number of patients	139	164	
Male/female	61/78	69/95	n.s.
Age	33.1 ± 13.2	34.8 ± 14.1	n.s.
Years until TSP therapy	6.9 ± 6.8	5.3 ± 5.2	0.02
Proteinuria (g/day)	1.5 ± 1.6	0.8 ± 0.8	<0.0001
Hematuria (0: 1+: 2+: 3+)	11:19:33:76	4:28:42:90	n.s.
Systolic BP (mm Hg)	121 ± 15	119 ± 15	n.s.
Diastolic BP (mm Hg)	75 ± 15	72 ± 11	n.s.
Cr (mg/dl)	0.99 ± 0.40	0.87 ± 0.34	0.006
TP (g/dl)	6.6 ± 0.6	6.7 ± 0.6	n.s.
Pathological grade (I: II: III: IV)	5:14:64:56	7:47:64:46	0.0006
Prognostic score by Wakai et al. [7]	37.4 ± 17.8	28.1 ± 15.1	<0.0001

Analysis of factors predicting resistance to TSP therapy

The CR rate was 54.1% in all patients ($N = 303$). In comparing data from patients in the non-CR and CR subgroups, a significant difference was observed in duration from diagnosis until TSP therapy (6.9 ± 6.8 versus 5.3 ± 5.2 years; $P = 0.02$), amount of proteinuria (1.5 ± 1.6 versus 0.8 ± 0.8 g/day; $P < 0.0001$), serum creatinine (0.99 ± 0.40 versus 0.87 ± 0.34 mg/dl; $P = 0.006$), pathological grade ($P = 0.0006$), and prognostic score (37.4 ± 17.8 versus 28.1 ± 15.1; $P < 0.0001$) (Table 3).

Table 4 Stepwise logistic regression analysis of non-CR 1 year after TSP therapy

	Coefficients	OR	95% CI	*P* value
Age at onset	−0.0330	0.97	0.95–0.99	0.003
Amount of urinary protein (log) (g/day)	0.4772	1.61	1.23–2.12	<0.001
Hematuria	−0.2731	0.76	0.56–1.04	0.08
Pathological grade	0.7604	2.14	1.50–3.06	<0.001
Intercept −0.1894				

Multivariate logistic analysis

The factors predicting resistance to TSP therapy were identified as age at onset, amount of proteinuria, hematuria grade, and pathological grade (Table 4). Resistance correlated positively with the score derived from the following formula: [(−0.0330) × (age) + (0.4772) × log (amount of urinary protein) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894].

Efficacy [3] and limitation of the resistance score

An ROC curve analysis revealed that patients with a resistance score of greater than −0.02 in the current study more easily resisted TSP therapy (sensitivity 69%, specificity 75%; Fig. 3).

Discussion

The present study demonstrates five points. The first is that about 600 IgA nephropathy patients per year received TSP

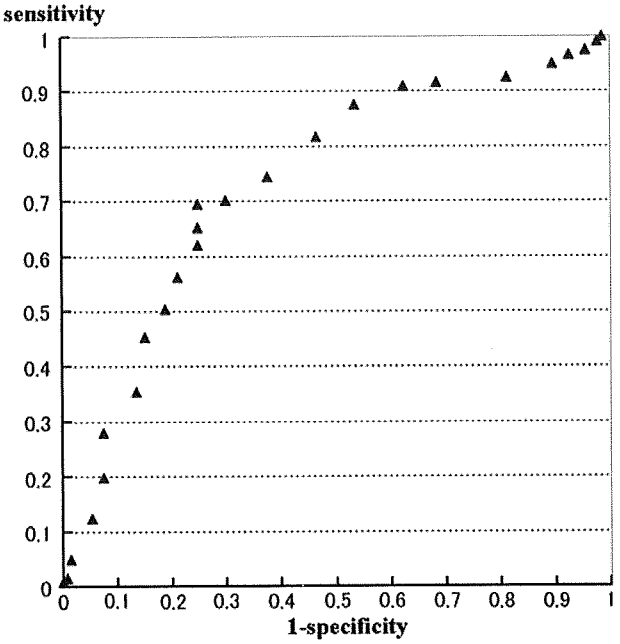

Fig. 3 Resistance correlated positively with the score derived from the following formula: [(−0.0330) × (age) + (0.4772) × log (amount of urinary protein) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894]. The cutoff value is −0.02, with a sensitivity of 69%, specificity of 75%, and positive likelihood ratio of 2.76

therapy in Japan since 2001, at which time the efficacy of TSP therapy was reported in an international journal. The second is that the CR rate 1 year after TSP therapy was almost 50%, which confirms the data of original report. The third is that CR rates ranged from 10% to 100% in each hospital that performed TSP therapy on at least ten patients. The fourth is that low- and high-CR-rate groups differed considerably in age at onset, amount of proteinuria, total protein, pathological grade, and Wakai et al. prognostic score. This suggests that the indication criteria for TSP therapy in the high-CR-rate group may differ from that in the low-CR-rate group. The fifth point is that the factors that predicted resistance to TSP therapy are age at onset, amount of proteinuria, hematuria grade, and pathological grade.

The aim of the present study, namely the identification of the factors predicting resistance to TSP therapy, differed from that of Hotta's original report, which aimed to establish which factors led to clinical remission in all IgA nephropathy patients. The present study revealed that younger patients with massive proteinuria, mild hematuria, and a severe pathological grade easily resist TSP therapy. It should be noted that these factors were already included in the prognostic scoring system developed by Wakai et al. Our results suggest that patients with late-stage or severe IgA nephropathy are likely to resist TSP therapy, and conversely patients with early or mild to moderate disease easily achieve CR following TSP therapy. An ROC curve of the predictive score for resistance to TSP therapy shows that, when the score is more than −0.02, the sensitivity is almost 70%, the specificity is 75%, and the positive likelihood ratio is 2.76. It is still unclear whether responsiveness to TSP therapy depends on how early the treatment is given, or on other factors, for instance genetic characteristics, or on a combination of these. A retrospective analysis by Hotta's group suggested that TSP therapy may be more effective for patients in the early stages of the condition, based on data that patients with serum creatinine level of less than 2.0 mg/dl responded well to the treatment [8]. There are several medical decisions; one is whether TSP therapy should be performed for patients with early or mild to moderate grade nephropathy so as to induce clinical remission, and the other is whether TSP therapy should be used for patients with a progressive type of IgA nephropathy. Further study should clarify the indications for TSP therapy in patients with IgA nephropathy.

Regarding clinical remission of urinary abnormalities, TSP therapy is still the most promising treatment, with a maximum CR rate of almost 50%, compared with 10–20% seen in steroid pulse therapy as reported by Pozzi et al. [3]. According to Hotta's original report about TSP therapy, the renal survival rate following treatment is estimated as 90% at 10 years, 71% at 16 years, and 66% at 20 years, with 48% (157/329) of patients achieving complete remission of urinary abnormalities and 52% (172/329) resisting the therapy. The fact that almost half of enrolled patients showed a poor prognosis demonstrates that TSP therapy is not a curative treatment for all patients with IgA nephropathy. Regardless, we must evaluate various therapies based on the renal survival rate after longer periods, such as 20 years, not on the CR rate assessed shortly after treatment. Further prospective randomized controlled trials in which the primary end point is the renal survival rate at 20 years, or cohort studies having large number of patients, are needed to clarify the efficacy of TSP therapy.

Acknowledgments We thank the Fellows of the Japanese Society of Nephrology who responded to our questionnaire. This work was supported by a grant (to H.I.) from the Progressive Renal Diseases Research Project of the Ministry of Health, Labour and Welfare of Japan. Drs. Kikuchi K, Ito Y, Yamaji I, Fukazawa S, Kawada T, Sakurai T, Wada A, Nagane Y, Sato H, Taguma Y, Wakui H, Konta T, Degawa N, Masakane I, Yamagata K, Kobayashi M, Ebihara I, Nakamura S, Oda T, Tukamoto Y, Ishizuka A, Shiraga H, Imasawa T, Seki T, Takemoto F, Matsushita K, Shibata T, Murakami M, Takahashi T, Wakai S, Ando M, Mishio Y, Hayashi M, Sasaki S, Okada T, Nitta K, Higuchi C, Funahiki K, Tamura K, Yasuda H, Yoshimura A, Takizawa R, Suwabe T, Hayaasa J, Yokota S, Sato M, Jinguuji Y, Higuchi M, Nakao I, Yoshida H, Araki H, Yoshimura M, Wada T, Koni I, Yamamoto T, Kasai K, Tomita M, Fukuda M, Inaguma D, Naruse T, Yamashita H, Asada Y, Sugimoto T, Isono M, Mukoyama M, Mori Y, Komatsu H, Tsuji H, Ishimura E, Imai E, Inoue T,

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Conflict of interest statement None declared.

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ORIGINAL ARTICLE

Ultrasonography as a predictor of overt bleeding after renal biopsy

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Abstract
Background Renal biopsy is essential for the diagnosis of kidney diseases, but complications, particularly bleeding incidents, remain problematic.
Methods To evaluate the frequency of renal biopsy complications, and to reveal clinical and laboratory factors associated with overt bleeding complications, focusing on those available at hospital ward, we conducted a retrospective observational study for the period between 2001 and 2005 at Mie University Hospital in patients who underwent percutaneous renal biopsy of a native kidney. Of a total of 323 patients, 317 met the inclusion criteria.
Results Only one patient (0.3%) required blood transfusion or intervention to stop bleeding. The mean decrease in hemoglobin (Hb) after biopsy was 0.43 ± 0.7 g/dL. Hb decreased ≥1.0 g/dL in 66 patients (20.8%) and ≥10% in 32 patients (10.1%). On ultrasonography, perirenal hematoma was detected immediately after biopsy in 273 patients (86.1%), and 41 patients (12.9%) showed hematoma ≥2 cm in width. Analgesics were required for back pain in 67 patients (21.1%). Vasovagal response developed in 31 patients (9.8%). Macrohematuria occurred in 12 patients (3.8%). Urinary catheter was used in 161 patients (50.8%). For Hb decrease ≥10% after biopsy, multivariate analysis revealed perirenal hematoma (≥2 cm) as a significant factor. Other significant factors were prolonged international normalized ratio of prothrombin time, elevated blood pressure on hospital admission, older age, increased serum creatinine level, and steroid use.
Conclusion Perirenal hematoma ≥2 cm on ultrasonography immediately after biopsy might well represent a predictive factor for bleeding complications.

Keywords Renal biopsy · Bleeding complication · Minor complication · Hematoma · Ultrasonography · Incidence of renal biopsy

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Introduction

Since the first report by Iversen in 1951 [1], renal biopsy has become a valuable method not only for the diagnosis of kidney disease, but also to decide treatment strategy, assess prognosis, and evaluate response to treatment [2]. However, renal biopsy is still associated with complications, including bleeding, macroscopic hematuria, fever, infection, and renal arteriovenous fistula. Although rare, serious complications may require nephrectomy or even result in death [3–6]. Technical advances such as use of automated biopsy needle under ultrasonographic guidance have improved the safety of renal biopsy [7], but life-threatening hemorrhagic complications still occur in some patients, and careful monitoring is thus required after renal biopsy. Generally suggested risk factors for bleeding complications include hypertension, thrombocytopenia, prolonged bleeding time, coagulation factor abnormalities, renal dysfunction, repeated punctures, and amyloidosis [7–12]. In addition, milder complications after renal biopsy, including back pain and transient hypotension due to vasovagal responses, have often been omitted from previous reports, so incidences remain unclear.

This retrospective study surveyed complications after renal biopsy performed over a 5-year period at our hospital to evaluate the true incidence of complications, including milder complications. We also investigated clinical and laboratory factors associated with severity of bleeding after renal biopsy. For nephrologists, it is important to predict bleeding complications soon after the biopsy procedure. Therefore, we focused only on factors which are available at the hospital ward.

Materials and methods

Patient population

This retrospective study initially enrolled 323 consecutive patients who had undergone percutaneous renal biopsy at Mie University Hospital between January 2001 and November 2005. Data were analyzed for 317 patients, after excluding 2 patients with insufficient data and 4 patients who had received blood transfusion prior to biopsy.

Assessment of renal biopsy complications

Laboratory data and complications were retrospectively analyzed by reviewing medical records. Evaluation of renal biopsy complications included changes in hemoglobin (Hb) values and need for blood transfusions or other interventions for hemostasis. Other complications assessed were macroscopic hematuria, back pain requiring use of analgesics, infection, and use of a urinary catheter.

Assessment of clinical factors

Clinical factors evaluated in association with changes in Hb after renal biopsy included sex, age, body mass index, blood pressure on hospital admission, postbiopsy blood pressure, blood urea nitrogen (BUN), creatinine (Cr), albumin (Alb), creatinine clearance (Ccr), Hb, platelet count, international normalized ratio of prothrombin time (PT-INR), urinary protein, number of punctures for biopsy, size of hematoma after biopsy, macroscopic hematuria after biopsy, clinical diagnosis before biopsy, and steroid use at biopsy.

Assessment of perirenal hematoma

Perirenal hematoma size after biopsy was measured by ultrasonography. Maximum width of perirenal hematoma 10 min after biopsy was classified into three categories: no hematoma; <2 cm; and ≥ 2 cm.

Assessment of bleeding complications

Serious bleeding complications were defined by need for blood transfusion or other intervention for hemostasis. In addition, overt bleeding complications were defined in patients with Hb decrease $\geq 10\%$ on the morning after biopsy (i.e., after 16–18 h). A percentage decrease was used rather than an absolute difference in Hb as patients with lower baseline Hb before biopsy were more susceptible to the effects of a further drop in Hb due to biopsy. In other words, even with the same Hb decrease of 1 g/dL, a patient with baseline Hb of 7 g/dL was more likely to display serious symptoms of anemia than a patient with baseline Hb of 14 g/dL.

Renal biopsy protocols

In brief, the renal biopsy protocol at our hospital during the investigated period was as follows. All patients were hospitalized. Antiplatelet drugs were discontinued 1 week before biopsy. Medical history for infections and blood type, complete blood count (CBC), clinical chemistry, and clotting parameters were determined the day before biopsy. A peripheral intravenous line was kept before biopsy, and a single dose of a first-generation cephalosporin antibiotic was administered intravenously. Renal biopsy was performed at about 14:00 under ultrasonographic guidance with 18G automated biopsy needle. In general, three samples of renal tissue were obtained. Renal biopsy was performed by a nephrologist or an internist with ≥ 3 years of experience under the direction of a nephrologist. Firm pressure was applied for 10 min after biopsy to treat bleeding, then the patient was returned to their room, a pressure dressing was applied, and the patient was kept in a supine resting position. Hemostatic agent (tranexamic acid) was used only when necessary for bleeding complications. Vital signs were checked hourly, and a CBC was performed after about 4 h. If no problems were identified, the patient was allowed to raise the knee on the side contralateral to the biopsy and the pressure dressing was partially removed. About 7 h after biopsy (before lights were turned off), the patient was allowed to lie in a decubitus, biopsy-side-down position. The patient then remained at rest during the night and was observed. Urinary catheter was inserted if the patient had not spontaneously voided before lights were turned off or if needed and requested by the patient. The next morning (about 16–18 h after biopsy), vital signs, CBC, a check for macroscopic hematuria, and ultrasonography (to measure hematoma size) were performed. If there were no problems, the patient was allowed to get out of bed. However, the day after biopsy, patients were instructed to rest in bed as much as possible except to use the bathroom. Patients were instructed to avoid running

up stairs or other activities where they might injure their back for 1 week after biopsy.

Statistical methods

Binary variables were analyzed using χ^2 test, and continuous variables were analyzed by t test. After analysis of variance for comparison of three groups, Tukey's honestly significant difference (HSD) procedure was used to compare each group. Multivariate analysis was conducted using multiple logistic regression. Statistical significance was established at the $P < 0.05$ level. JMP5 software (SAS Institute Japan, Tokyo, Japan) was used for analysis.

Results

The 317 patients included for analysis comprised 171 men and 146 women, with mean age of 45 ± 18 years (range 13–82 years). The most common prebiopsy diagnosis was chronic glomerulonephritis ($n = 163$, 51.4%), followed by nephrotic syndrome ($n = 61$, 19.2%). Underlying disorders included diabetes mellitus ($n = 33$, 10.4%), rapidly progressive glomerulonephritis ($n = 20$, 6.3%), systemic lupus erythematosus ($n = 16$, 5.1%), acute glomerulonephritis ($n = 2$, 0.6%), and other ($n = 22$, 7.0%).

Table 1 lists the complications of renal biopsy. Only one patient (0.3%) required blood transfusion or other intervention to stop bleeding. No complications resulting in renal failure, nephrectomy or death were encountered. The morning after biopsy, mean decrease in Hb was 0.4 ± 0.7 g/dL. Hb decreased ≥1.0 g/dL in 66 patients (20.8%) and ≥10% in 32 patients (10.1%). Perirenal hematoma was detected immediately after biopsy in 273 patients (86.1%), with size <2 cm in 232 patients (73.2%) and ≥2 cm in 41 patients (12.9%). Analgesics for back pain after renal biopsy were required in 67 patients (21.1%). Transient hypotension due to vasovagal response developed in 31 patients (9.8%). Macrohematuria after biopsy occurred in 12 patients (3.8%). Urinary catheter was used in 161 patients (50.8%). Frequency of urinary catheter use was markedly higher in women (82%) than in men (24%). Other complications were abdominal pain and vomiting in eight patients, fever in four patients, headache in two patients, pulmonary embolus/renal vein thrombosis in two patients, and back pain/rebleeding 5 days after biopsy in two patients. Other complications included lancinating pain from the back to the lower extremity, dizziness, liver tissue sample, rash related to disinfectant used on the skin, acute prostatitis, and prolonged bed rest for 3 days due to enlarging hematoma, in one patient each.

Figure 1 depicts the relationship between percentage decrease in Hb the morning after biopsy and maximum perirenal hematoma size immediately after biopsy. In patients with hematoma ≥2 cm, mean decrease in Hb was 6.9 ± 7.3%, significantly greater than in patients with no hematoma, or hematoma <2 cm (2.0 ± 5.9%, 2.9 ± 5.1% respectively; $P < 0.01$).

Table 1 Complications of renal biopsy

Incident	*n*	%
Blood transfusion/intervention	1	0.3
≥1 g/dL decrease of Hb	66	20.8
≥10% decrease rate of Hb	32	10.1
Perirenal hematoma	273	86.1
≥2 cm	41	12.9
Lumbago or back pain	67	21.1
Vasovagal reflex	31	9.8
Macrohematuria	12	3.8
Use of urinary catheter	161	50.8

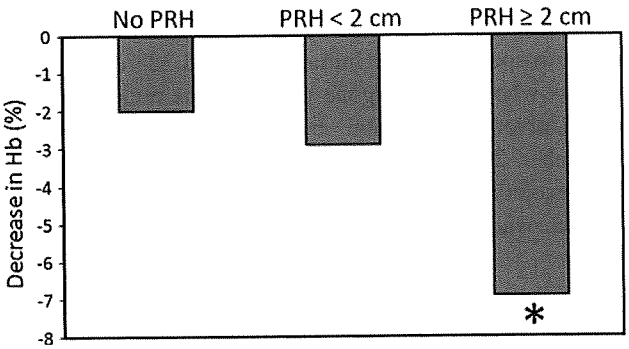

Fig. 1 In patients with hematoma ≥2 cm, mean decrease in Hb was significantly greater than in patients with no hematoma or hematoma <2 cm. *Significant difference between "No PRH" and "PRH < 2 cm" according to Tukey's HSD procedure ($P < 0.01$)

Next, we divided patients into two groups: those with Hb decrease ≥10% (overt bleeding complication group, as mentioned before) and those with Hb decrease <10% (control group). Table 2 summarizes the analyzed differences in baseline clinical factors. Compared with the control group, age, serum Cr, PT-INR, systolic and diastolic blood pressure on admission, and size of perirenal hematoma immediately after biopsy were significantly higher or greater in the overt bleeding complication group. In addition, renal function tended to be worse and steroid use tended to be higher in the overt bleeding complication group.

To examine factors related to decrease in Hb ≥ 10%, we performed logistic regression analysis using Hb decrease ≥10% (yes or no) as the dependent variable. Six explanatory variables were employed: age, serum Cr > 2.0 mg/dL (renal function), PT-INR > 1.0 (clotting function), mean blood pressure on admission >105 mmHg (blood pressure), size of perirenal hematoma immediately after biopsy ≥2 cm, and

Table 2 Differences in baseline clinical factors between overt bleeding group (Hb decrease ≥10%) and control group (Hb decrease <10%)

	Overt bleeding group (mean ± SD or %)	Control group (mean ± SD or %)	*P*
Sex (male, %)	46.9	54.7	0.398
Age (years)	51 ± 18	44 ± 18	0.028
Comorbidity (%)			
DM	6.3	10.9	0.416
SLE	6.3	4.9	0.743
BUN (mg/dL)	21.3 ± 12.4	18.2 ± 8.5	0.061
Cr (mg/dL)	1.5 ± 1.2	1.2 ± 0.6	0.019
Ccr (mL/min)	56 ± 30	65 ± 27	0.069
Hb (g/dL)	12.7 ± 2.1	12.4 ± 2.4	0.548
PLT ($\times 104/mm^3$)	25.2 ± 6.3	26.2 ± 8.5	0.518
PT-INR	1.02 ± 0.11	0.98 ± 0.09	0.020
Blood pressure on admission			
Systolic (mmHg)	137 ± 24	129 ± 20	0.032
Diastolic (mmHg)	83 ± 18	78 ± 12	0.019
Blood pressure after RBx			
Systolic (mmHg)	137 ± 25	130 ± 22	0.117
Diastolic (mmHg)	79 ± 14	77 ± 12	0.594
Proteinuria (g/day)	2.9 ± 3.2	2.6 ± 3.8	0.619
Punctures for biopsy (*n*)	3.0 ± 0.9	3.2 ± 0.9	0.340
Perirenal hematoma (≥2 cm, %)	43.8	9.5	<0.001
Steroid use (%)	31.3	17.9	0.069
Macrohematuria (de novo, %)	9.4	3.3	0.081

Hb hemoglobin, *DM* diabetes mellitus, *SLE* systemic lupus erythematosus, *BUN* blood urea nitrogen, *Cr* creatinine, *Ccr* creatinine clearance, *PLT* platelet count, *PT-INR* international normalized ratio of prothrombin time, *RBx* renal biopsy

Table 3 Multivariate analysis of clinical factors in the overt bleeding complication group (Hb decrease ≥10%)

	Odds ratio	95% CI	*P*
Perirenal hematoma (≥2 cm)	8.07	3.39–19.43	<0.001
PT-INR (≥1.0)	2.47	1.08–5.74	0.032
Mean blood pressure (≥105 mmHg)	2.54	1.06–6.02	0.034
Steroid use (yes)	2.59	1.02–6.35	0.039
Age (+1 year)	2.69	0.52–14.74	0.241
Cr (≥2.0 mg/dL)	1.41	0.43–4.08	0.544

CI confidence interval. Other abbreviations as per Table 2

use of steroids (Table 3). The strongest predictive factor for Hb decrease ≥10% was perirenal hematoma ≥2 cm (odds ratio 8.07; 95% confidence interval 3.39–19.43). Other significant risk factors were PT-INR, mean blood pressure on admission, and steroid use. Age and serum Cr showed no significant differences.

Discussion

Complications of renal biopsy include macroscopic hematuria, microscopic hematuria, perirenal hematoma, renal arteriovenous fistulas, infection, and pain [5, 12, 13]. A survey conducted by the Japanese Society of Nephrology in 2001 of medical centers throughout Japan estimated that 9,700 renal biopsies are performed annually. The incidence of serious events requiring blood transfusion or another intervention was 1.8/100 patients, and two deaths were reported over a 3-year period [5]. The frequency of serious events requiring transfusion or other intervention reported overseas is 0.4–6% [10, 12–14].

In our retrospective study of bleeding complications with renal biopsy, only one patient (0.3%) required blood transfusion, and 32 patients (10.1%) showed Hb decrease ≥10%. In the patient requiring blood transfusion, angiography revealed pseudoaneurysm at the renal puncture site, and partial renal artery embolization was performed. No complications resulted in renal failure, nephrectomy or death. The rate of serious complications at our hospital was thus low, at 0.3%.

One of the most common complications of renal biopsy is perirenal hematoma. In general, postbiopsy perirenal hematoma is detected on ultrasonography in about 40% [11, 15] and on computed tomography in about 85% [16] of patients. In our hospital, hematoma was detected in 86.1% of patients overall on ultrasonography. Hematoma size was ≥2 cm in 12.9% of patients, and the percentage decrease in Hb was significantly greater in this subgroup than in

patients without hematoma (Fig. 1). In a previous study using the same size of needle (18G), incidence of hematoma ≥2 × 2 cm was reportedly 2.2% [13]. The higher incidence of hematoma in our study may be attributable to several factors, including differences in indications for performing renal biopsy, easier detection of smaller hematomas when comparing findings before and just after renal biopsy, and advances in ultrasound technology. Hematoma size correlated with percentage decrease in Hb. This makes evaluation of perirenal hematoma after renal biopsy useful in predicting bleeding complications.

Even without overt complications after renal biopsy, Hb decreases by ≥1 g/dL in 46% and ≥2 g/dL in 9.6% of patients [14]. This is due to many factors, including hemodilution with administration of intravenous fluids, positional changes (recumbency), and stimulation of antidiuretic hormone secretion by pain [10, 14]. In our study, 66 patients (20.8%) showed ≥1 g/dL decrease in Hb. Another factor may have been needle size (14G in published report [14]; 18G at our hospital).

Macroscopic hematuria after biopsy occurred in 12 patients (3.8%), a lower frequency than reported elsewhere (6–8%) [11, 17]. The low incidence of macrohematuria in our patients may be attributable to use of a relatively small needle.

Back pain and transient hypotension due to vasovagal response are not unimportant complications, but accurate incidences have not previously been reported. In this study, 21.1% of patients experienced back pain requiring analgesic therapy after biopsy. Causes of back pain may include biopsy puncture, perirenal hematoma, and forced bed rest after biopsy. Back pain is an important clinical sign of enlarging hematoma. Forced long-term bed rest can be a potential cause of pain, particularly back pain and lumbago, and may mask the signs of progressive perirenal bleeding. Most back pain in our cases resulted from forced bed rest (data not shown). In Japan, complete bed rest after renal biopsy is the standard of care, and mean duration of forced supine position is reportedly 12 h [5]. Another cause of back pain after biopsy in Japan may be the use of sand bags or abdominal compression belts that compress the kidney through the back side. Sand bags and compression belts do not seem to be used in other countries, so this will represent the next focus of clinical research.

Transient hypotension due to vasovagal response occurred in 9.8% of patients, but this was safely treated with fluid replacement and/or intravenous atropine sulfate in all cases.

Other complications with low incidence, but that cannot be disregarded, were pulmonary embolism and renal vein thrombosis. Patients with nephrotic syndrome or who are otherwise treated with steroids generally display hypercoagulability. Increased risk of thrombosis in these patients with prolonged bed rest must be kept in mind. Urinary catheter was used in about 50% of patients, but in our hospital this is usually performed at the request of patients, or when no voluntary voiding is seen by 6 h after biopsy. The Japanese Guidebook of the Renal Biopsy [5] advices nephrologists to use urinary catheter to make biopsied patient keep resting, but reduced use of urinary catheterization should be a future consideration to reduce patient burden and prevent urinary tract infection.

Previously reported factors related to bleeding complications after renal biopsy include thrombocytopenia, prolonged bleeding time, clotting abnormalities [abnormal partial thromboplastin time (PTT) and prothrombin time], hypertension, renal dysfunction, sex (female), age (younger), biopsy needle size (larger), equipment (nonuse of automated biopsy needle), repeated biopsy puncture, and amyloidosis [7–12].

In this retrospective study, perirenal hematoma ≥2 cm immediately after biopsy was the strongest predictor of more severe anemia the morning after biopsy. Our findings concur with other reports of progressive anemia with larger postbiopsy hematoma [11]. This indicates that ultrasonographic evaluation of hematoma size immediately after renal biopsy is useful in predicting potentially severe blood loss. Patients with perirenal hematoma ≥2 cm require particularly careful monitoring.

Other factors associated with more severe progressive anemia after renal biopsy include clotting factor abnormalities, elevated blood pressure on admission, use of steroids, older age, and renal dysfunction.

Clotting abnormalities are a risk factor for increased bleeding [12]. In our study, prolonged PT-INR was associated with greater decrease in Hb. Evaluation of clotting function prior to renal biopsy is essential.

In the evaluation of hypertension, mean blood pressure of 105 mmHg lies within the upper quartile. This corresponds to systolic blood pressure of 140 mmHg and diastolic blood pressure of 90 mmHg. In contrast with a relationship between admission blood pressure and Hb decrease, no significant relationship was seen between postbiopsy blood pressure and Hb decrease. However, stress-induced changes in blood pressure just before and after renal biopsy may affect accurate assessment of blood pressure. In addition, bleeding may be affected by vascular factors other than blood pressure. Irrespective of blood pressure at time of renal biopsy, however, patients with history of hypertension are at increased risk of bleeding complications [10]. History of hypertension and blood pressure on admission are important clinical information when performing renal biopsy.

To the best of our knowledge, increased postbiopsy bleeding complications in patients using steroids have not been reported previously. The original disease, for example,

active collagen disorders and systemic vasculitis, could affect the bleeding phenomenon at the puncture sites. Increased blood pressure is another common adverse effect of steroids [18, 19]. In addition, long-term steroid use increases skin and superficial vessel fragility. These are all factors potentially associated with greater decrease in Hb, although precise bleeding mechanism caused by steroids is still unclear.

Studies of correlations between renal dysfunction and bleeding complications after renal biopsy have shown higher risk with serum Cr > 2.0 mg/dL [10] and Cr ≥ 5.0 mg/dL [14]. In this study, serum Cr was significantly higher in the overt bleeding complication group than in the control group, but no significant difference in Ccr were identified. Multivariate analysis examining other factors showed no significant correlation between Hb decrease and serum Cr.

Age was higher in the overt bleeding complication group, but stratified analysis for patients <65 years or ≥65 years showed no significant difference between the two subgroups (data not shown). Increased bleeding complications have previously been reported in younger patients [12], but mean age of our patients was higher, and differences in definition of bleeding complications may have contributed to discrepancy in these results. Moreover, blood pressure is usually higher in older patients, which can make age a confounding factor.

No relationships were apparent between Hb decrease and platelet count, sex, number of biopsy punctures or underlying disease.

In addition to those consisting of clinical information available at the hospital ward, we also found some positive relationship between Hb decrease and depth of needle insertion, length of obtained renal specimen, and included large vessels. In particular, length of medulla was well correlated with size of hematoma and Hb decrease (data not shown). Koumoto had already reported similar relationship during the old period when Silverman needle and Tru-Cut needle were used for renal biopsy [20]. Nephrologists should be cautious of depth of needle insertion to avoid major hemorrhage complication. This issue will be discussed on another occasion.

Hb decrease ≥10% was used to define the overt bleeding complication group, but whether this accurately predicts serious bleeding complications is unknown. Incidence of serious bleeding complications was also low (only one patient over a 5-year period), making relevant factors difficult to evaluate accurately. Hb decrease ≥10% has been used in another study to evaluate bleeding complications [10]. Patients with larger decreases in Hb require more intensive clinical monitoring. Prediction of high risk for bleeding complications immediately after renal biopsy is thus clinically significant.

The present study was conducted as a retrospective review. Some mild complications may not have been reported, contributing to data bias. Incidence of complications might thus have been underestimated. In addition, the study analyzed a relatively small number of patients at a single medical center. Whether our results can be extrapolated to other medical facilities is unclear. Further investigation of bleeding complications after renal biopsy in a multicenter prospective study with relevant endpoints is necessary.

Conclusion

Our study of renal biopsy complications revealed serious bleeding complications in only one patient (0.3%), whereas milder complications such as perirenal hematoma and back pain were common. Ultrasonography immediately after renal biopsy to evaluate perirenal hematoma was useful in predicting further bleeding complications. Other factors indicating a need for more intense monitoring of bleeding complications immediately after renal biopsy included clotting factor abnormalities, elevated blood pressure on admission, use of steroids, older age, and renal dysfunction.

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ORIGINAL ARTICLE

How long is strict bed rest necessary after renal biopsy?

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Abstract
Background No consensus exists on the amount of bed rest required after renal biopsy. Moreover, forced prolonged bed rest can be uncomfortable in patients undergoing renal biopsy.
Objective To evaluate whether the length of strict bed rest affects the incidence of pain and other complications after renal biopsy.
Study design, facility, and patients This single-center retrospective observational study was conducted in 94 consecutive patients undergoing biopsy of a native kidney between November 2005 and December 2006 at Mie University Hospital. The control group was composed of 317 patients who underwent biopsy of a native kidney between January 2001 and October 2005.
Methods The incidence of biopsy-related complications was compared between two periods of strict bed rest: 2 h of strict bed rest with no abdominal bandage (November 2005 to December 2006) and 7 h of strict bed rest with an abdominal bandage (January 2001 to October 2005). The primary outcome was the incidence of back pain requiring analgesics. The secondary outcomes were: need for transfusion or hemostatic intervention, decrease of $\geq$10% in hemoglobin (Hb) after biopsy, macroscopic hematuria, infection possibly related to biopsy, need for single or indwelling bladder catheterization, and other biopsy-related complications.
Results The incidence of back pain requiring analgesics decreased with a shorter period of strict bed rest [7.5% versus 21.1%, odds ratio (OR) 0.30, 95% confidence interval (95% CI) 0.12–0.64, $p = 0.004$]. Even after adjustment for age, sex, perinephric hematoma size, and number of biopsy punctures, the incidence of back pain decreased significantly (OR 0.34, 95% CI 0.14–0.73, $p = 0.01$). With a shorter period of strict bed rest, there were no significant differences in bleeding complications (need for transfusion or other hemostatic intervention), decrease of $\geq$10% in Hb or macroscopic hematuria. However, the need for indwelling bladder catheterization decreased significantly (36.2% versus 50.5%, OR 0.55, 95% CI 0.34–0.88, $p = 0.013$).
Conclusions Shortening the period of strict bed rest after renal biopsy from 7 h to 2 h decreased the incidence of back pain, but there was no increase in bleeding or other biopsy-related complications. Our findings suggest that a shorter period of strict bed rest can safely reduce discomfort in renal biopsy patients.

Keywords Renal biopsy · Bed rest · Bleeding complication · Back pain · Quality of life

Introduction

Since first reported by Iversen et al. in 1951 [1], renal biopsy has been established as a useful procedure not only for diagnosis of kidney disease, but also to determine treatment strategy, assess prognosis, and evaluate therapeutic response [2]. With advances in technology such as ultrasound-guided and automated needle biopsy [3], renal biopsy has become safer, but life-threatening bleeding complications still occur in a small number

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of cases. Therefore, careful postbiopsy monitoring is essential.

Nevertheless, no consensus exists on bed rest procedures after renal biopsy. Some authors advocate same-day renal biopsy with strict bed rest for 6 h [4–7], whereas others advocate postbiopsy monitoring for 24 h, citing a fairly high incidence of serious bleeding complications between 6 and 24 h [8]. In Japan, renal biopsy is generally performed as an inpatient procedure. Standard postbiopsy care includes sandbag compression for 2–8 h, strict bed rest for 6–12 h, and ambulation after 18–24 h [9]. In our medical center, between 2001 and 2005, we used an abdominal compression bandage, strict bed rest for 7 h, and further bed rest for 11 h. However, there was a high (21.1%) incidence of back pain after renal biopsy requiring analgesics [10]. This suggests that prolonged forced bed rest may contribute to patient discomfort.

Therefore, we conducted this study to examine whether shortening the period of strict bed rest can safely reduce patient discomfort, but without increasing other complications.

Patients and methods

This study enrolled 94 consecutive patients undergoing biopsy of a native kidney between November 2005 and December 2006 at Mie University Hospital. The control group originally included 323 consecutive patients who underwent biopsy of a native kidney between January 2001 and October 2005, but 2 had insufficient data and 4 required transfusions before biopsy, so data from 317 control patients were analyzed.

The study was designed as a single-center retrospective observational study (comparison with historical controls). The incidence of postbiopsy complications was compared between two different bed rest procedures: 2 h of strict bed rest with no abdominal bandage (November 2005 to December 2006) and 7 h of strict bed rest with an abdominal bandage (January 2001 to October 2005). The primary outcome was the incidence of back pain requiring analgesics. The secondary outcomes were: need for transfusion or hemostatic intervention, decrease of $\geq$10% in hemoglobin (Hb) after biopsy, macroscopic hematuria, infection possibly related to biopsy, need for single or indwelling bladder catheterization, and other biopsy-related complications.

Patient factors evaluated for an association with postbiopsy complications included: age, sex, body mass index, blood pressure on hospital admission, laboratory test values [blood urea nitrogen (BUN), creatinine, albumin, creatinine clearance, Hb, platelet count, and prothrombin time–international normalized ratio (PT-INR)], proteinuria, number of biopsy punctures, hematoma size just after biopsy, macroscopic hematuria after biopsy, prebiopsy clinical diagnosis, and steroid use just before biopsy. The above laboratory test values were those before biopsy.

Hematoma size just after biopsy was measured by ultrasound. Maximum perinephric hematoma size following 10 min of compression hemostasis after biopsy was classified into three categories: none, <2 cm, and $\geq$2 cm.

All patients were hospitalized for biopsy. Standard guidelines for renal biopsy at our medical center were as mentioned previously [10]. Antiplatelet or anticoagulant drugs were discontinued 1 week before biopsy. Renal biopsy was performed by the same methods in the groups with 2 and 7 h of strict bed rest under ultrasonographic guidance with an 18G automated biopsy needle. Changes went into effect in November 2005; an abdominal compression bandage after renal biopsy was no longer used, and the period of strict bed rest was shortened from 7 to 2 h. For 2 h after biopsy, patients were placed in a lateral decubitus position (with the biopsy side down); after 4 h, Hb was checked, and if no problems occurred, the head of the bed was elevated to 30° and patients were allowed to turn over. If patients did not void spontaneously before lights were turned off, or at patient request, single or indwelling bladder catheterization was performed as needed. The next morning (about 18 h later), vital signs were taken, Hb was measured, an ultrasound was performed to evaluate perinephric hematoma size, and presence or absence of macroscopic hematuria was noted. If there were no problems, the patient was allowed out of bed.

In this study, back pain was defined as pain during bed rest after renal biopsy that required analgesic therapy. The criteria to use analgesics in our department was as followed: when biopsied patients complained of lumbago or back pain during bed rest, attending physician or doctor on duty checked their bleeding sign by physical examination and, if necessary, complete blood count test or ultrasonography of biopsied kidney. If the pain was not a bleeding sign and the patient could not endure the pain, then physicians prescribed analgesics such as orally or suppository administered acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or subcutaneous injection of pentazocine HCl. The choice and dosage of analgesic were decided by physicians. Transfusion or hemostatic intervention was defined as any transfusion or procedure such as angiography or renal artery embolization required for treatment of anemia due to bleeding after renal biopsy. A decrease in Hb of $\geq$10% by the morning after biopsy was considered to be a potential risk factor of bleeding complications. The reason for using percentage decrease rather than absolute decrease in Hb was as described before [10]. Macroscopic hematuria was defined as a newly developed macroscopic hematuria anytime during the follow-up observation period.

Statistical analysis

Categorical (two-value) variables were analyzed by χ^2 test, and continuous variables were analyzed by t test. Multivariate analysis was performed using multiple logistic regression analysis. The level of statistical significance was $p < 0.05$. Analysis was performed using JMP5 (SAS Institute, Tokyo, Japan).

Ethical considerations

A verbal explanation was given and written consent was obtained from all patients prior to renal biopsy. This study was approved by the ethics committee of Mie University School of Medicine.

Results

Table 1 shows the patient clinical characteristics in the 2 h strict bed rest group (short bed rest group) and the 7 h strict bed rest group (long bed rest group). There were no significant differences in age, sex, mean blood pressure on hospital admission, baseline Hb value, platelet count or PT-INR. Although the number of renal biopsy punctures did not differ, the number of samples obtained was higher in the long bed rest group (2.7 ± 0.5) than in the short bed rest group (2.5 ± 0.6) ($p = 0.012$). Use of steroids just prior to renal biopsy or hemostatic agents during biopsy did not differ between the groups. Perinephric hematoma size after renal biopsy, as determined by ultrasound, did not significantly differ between the groups (none, <2 cm, ≥2 cm: short bed rest group: 8%, 80%, 12%, respectively; long bed rest group: 14%, 73%, 13%, respectively).

Table 1 Patient characteristics

	2 h strict bed rest	7 h strict bed rest	p
No. of patients	94	317	
Age (years)	46 ± 19	45 ± 18	0.682
Sex (M:F)	57:37	171:146	0.251
Mean BP (mmHg)	94 ± 17	95 ± 14	0.258
Hb (g/dl)	12.5 ± 2.4	12.5 ± 2.4	0.548
PLT ($\times 10^4/\mu l$)	25.3 ± 6.7	26.1 ± 8.3	0.191
PT-INR	0.99 ± 0.10	0.99 ± 0.09	0.613
No. of punctures	3.5 ± 1.5	3.2 ± 0.9	0.993
No. of samples	2.5 ± 0.6	2.7 ± 0.5	0.012
Steroid use (%)	10.6	19.2	0.053
Use of hemostatic agent (%)	2.1	1.3	0.539
Hematoma size after biopsy (0/<2 cm/≥2 cm) (%)	8/80/12	14/73/13	0.369

Table 2 Incidence of biopsy-related complications

	2 h strict bed rest	7 h strict bed rest	OR (95% CI)	p
Back pain requiring analgesics	7.5%	21.1%	0.30 (0.12–0.64)	0.004
Transfusion/ hemostatic intervention	2.1%	0.3%	6.87 (0.65–149)	0.117
Decreased Hb ≥ 10%	7.5%	10.1%	0.72 (0.28–1.59)	0.444
Macroscopic hematuria	4.3%	3.8%	1.13 (0.31–3.33)	0.836
Urethral catheterization	36.2%	50.8%	0.55 (0.34–0.88)	0.013
Infection	2.1%	1.3%	1.13 (0.16–4.99)	0.885

The incidence of back pain was significantly lower in the short bed rest group (7.5%, 7/94 patients) than in the long bed rest group (21.1%, 67/317 patients) [odds ratio (OR) 0.30, 95% CI 0.12–0.64, $p = 0.004$] (Table 2). Even after adjustment for age, sex, perinephric hematoma size, and number of biopsy punctures, the incidence of back pain was significantly lower in the short bed rest group (OR 0.34, 95% CI 0.14–0.73, $p = 0.01$).

Transfusion or hemostatic intervention was required in one patient (0.3%) in the long bed rest group and in two patients (2.1%) in the short bed rest group ($p = 0.117$).

By the morning after renal biopsy, Hb decreased by ≥10% in 7 of 94 patients (7.5%) in the short bed rest group and in 32 of 317 patients (10.1%) in the long bed rest group. There was no significant difference (OR 0.72, 95% CI 0.28–1.59, $p = 0.444$). There was also no significant difference in macroscopic hematuria between the short bed rest group (4.3%) and long bed rest group (3.8%) (OR 1.13, 95% CI 0.31–3.33, $p = 0.836$).

The incidence of single or indwelling bladder catheterization was significantly lower in the short bed rest group (36.2%) than in the long bed rest group (50.5%) (OR 0.55, 95% CI 0.34–0.88, $p = 0.013$). The incidence of infection did not differ significantly between the short bed rest group (2.1%) and long bed rest group (1.3%) ($p = 0.885$, Table 2).

Other postbiopsy complications included vasovagal reactions and gastrointestinal symptoms such as abdominal pain and nausea in a few patients in the short bed rest group. However, there were no complications with a higher incidence than in the long bed rest group. In the short bed rest group, one patient did not comply with strict bed rest.

Discussion

Shortening the period of strict bed rest after renal biopsy significantly reduced the incidence of back pain requiring