Effects of a Novel Piezo Actuator-driven Pulsed Water Jet System on Residual Kidney After Partial Nephrectomy in a Rat Model

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OBJECTIVE To evaluate renal damage after off-clamp partial nephrectomy (PN) using a novel surgical device, piezo actuator-driven pulsed water jet (ADPJ) system.

METHODS Sprague-Dawley rats were divided into 4 groups and subjected to sham operation, off-clamp PN by the piezo ADPJ system, radio knife, and soft coagulation, which have been used as thermal coagulation devices. Urine and blood samples were collected, and residual kidneys were harvested at 1, 7, 14, 30, and 90 days after PN. Serum blood urea nitrogen, creatinine, and urinary and serum kidney injury molecule-1 KIM-1 levels were measured. Morphological features and the extent of renal ischemia of resection surfaces were evaluated by hematoxylin-eosin staining and immunostaining using antibodies to 1-methyladenosine, respectively. In addition, the expression levels of KIM-1 mRNA extracted from each resection surface were analyzed by quantitative real-time reverse transcription polymerase chain reaction.

RESULTS Serum blood urea nitrogen and creatinine were significantly lower with the piezo ADPJ system than with soft coagulation. Urinary and serum KIM-1 levels were also significantly decreased with the ADPJ. The extent of 1-methyladenosine immunostaining was significantly less with the ADPJ than with thermal coagulation devices. The expression levels of KIM-1 mRNA were also lower in the ADPJ system group.

CONCLUSION The piezo ADPJ system might attenuate renal damage after off-clamp PN. UROLOGY 123: 265−272, 2019. © 2018 Elsevier Inc.

The incidental finding of renal cell carcinomas has recently become more common because of advances in noninvasive diagnostic techniques including ultrasonography, computed tomography, and magnetic resonance imaging.[1,2] Partial nephrectomy (PN) has become the gold standard for treatment of small or localized renal cell carcinomas.[3,4] Emerging evidence for the relationship between chronic kidney disease (CKD) and life-threatening cardiovascular disease indicates the importance of preserving postoperative renal function, in addition to controlling the oncological outcome.[5] Renal hilar clamping to provide a relatively bloodless surgical field, thermal coagulation, and sutured renorrhaphy for hemostasis are generally performed for PN. However, hilar clamping and sutured renorrhaphy have been reported to cause renal ischemia, resulting in postoperative renal dysfunction.[6]

Recently, off-clamp and selective clamp PN have been performed.[7] However, the approach is influenced by tumor location and operator skill, and it remains challenging because of its massive bleeding. Moreover, thermal coagulation might cause postoperative renal damage, but the hazards of thermal coagulation have not been reported. To preserve postoperative renal function, a novel surgical device is needed to safely perform off-clamp, nonthermal, and nonsuturing PN.

We have developed a novel surgical device, a piezo actuator-driven pulsed water jet (ADPJ) system,[8] that can

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dissect tissues while preserving fine blood vessels and causing no thermal injury. Compared with conventional continuous water jet systems, the ADPJ system offers an intermittent water flow, contributing to dissection at a constant depth and decreases in water volume by combining a quarter quantity of water and air bubbles, which could achieve clearer operative views. We have reported the safety of off-clamp open PN using this system in swine.[9] Next, we invented the prototype laparoscopic ADPJ system and could perform off-clamp laparoscopic PN safely in swine.[10] Importantly, there was little renal damage using the laparoscopic ADPJ compared with other thermal coagulation devices in the postoperative acute phase. Thus, to clarify longer-term renal function after PN, the renal damage after off-clamp PN using the ADPJ system was evaluated in a rat model.

MATERIALS AND METHODS

Off-Clamp PN in Rats

In this study, rats were used because of the number of animals needed to evaluate renal function and histological changes after PN. A total of 100 male Sprague-Dawley rats weighing 214-354 g were divided into 4 groups and subjected to sham operation, off-clamp PN with the ADPJ system (Fig. 1A), radio knife (Diatermo MB122K, Gessate, GIMA, Italy; Monopolar COAG mode, 14 V), and soft coagulation (VIO, 200S system, ERBE Elektromedizin, Tübingen, Germany; effect 3, Max 30 W) (n = 25 in each group). There were no differences of mean body weight between the groups. The sample size of 5 rats in each group was estimated to achieve 80% power of detecting a difference at the 5% level of 2-sided significance. The rats were anesthetized with inhalation of an isoflurane anesthesia apparatus (NARCOBIT-E, Natsume Seisakusho Co. Ltd., Toyo, Japan). In the sham group, rats underwent unilateral nephrectomy. In the ADPJ group, after the nephrectomy, the contralateral renal capsule was cut by micro scissors, and the renal parenchyma was dissected by the ADPJ system (Fig. 1B). The input voltage was fixed at 25 V, which corresponded to 1.0 MPa,[9] and the ADPJ system delivered 4 mL/min of saline solution from the tip of the nozzle at a frequency of 400 Hz as pulsed flow. Preserved fine blood vessels using the ADPJ system were coagulated by bipolar coagulation (SurgiStat II, 30 V, Valley Labs, Boulder, CO), following cutting by micro scissors (Fig. 1C). The lateral and middle portion of the kidney was dissected using a ruler and the size of the removed kidney was $8 \times 8 \times 3$ mm^3, which means that normal kidney size was $20 \times 10 \times 7$ mm^3.

Similarly, in the radio knife group and the soft coagulation group, the renal parenchyma was dissected by micro scissors, and the resection surfaces were coagulated with a ball-type radio knife or paddle-type soft coagulation, respectively. Coagulation of the resected side was performed to the minimum necessary to

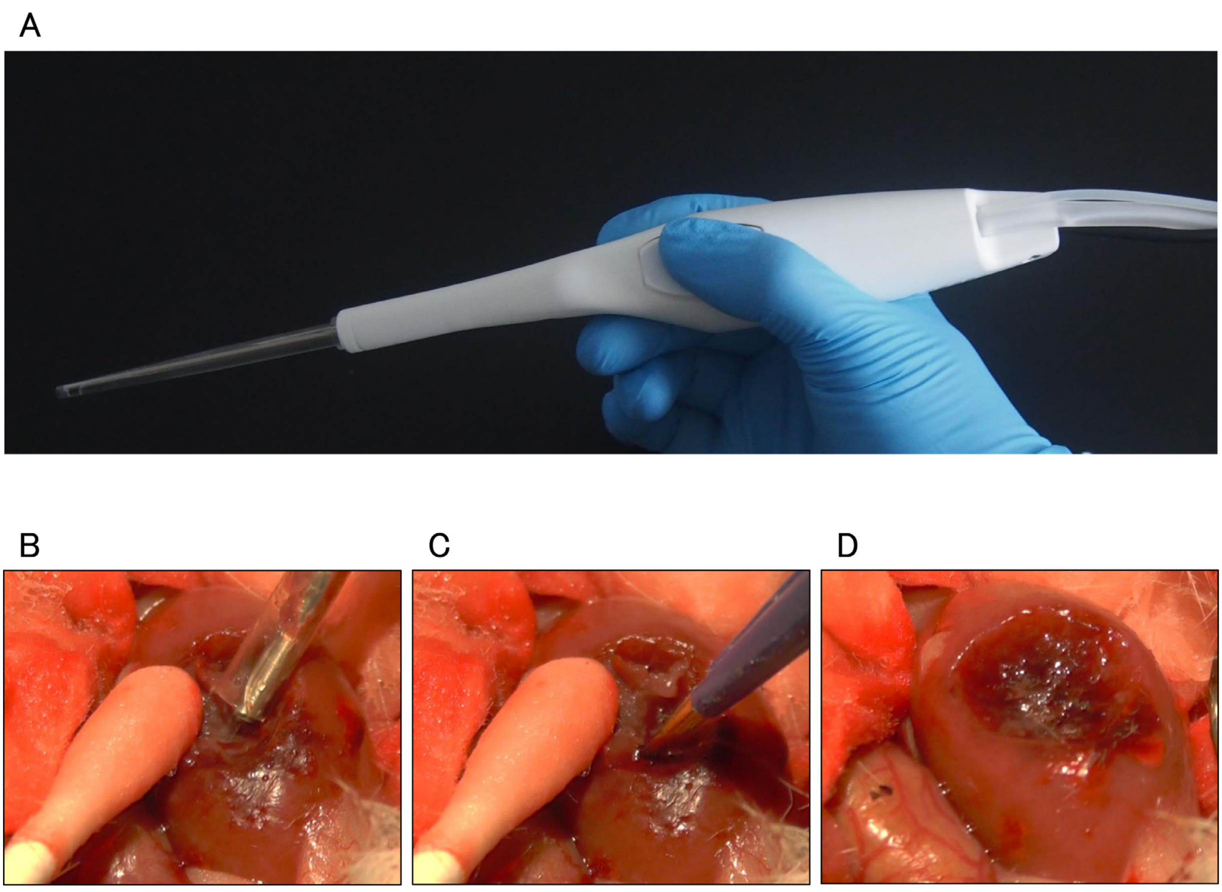

Figure 1. (**A**) Photograph of the piezo ADPJ system. (**B**) After resection of the renal capsule by micro scissors, renal parenchyma was dissected by the ADPJ system. (**C**) The preserved fine blood vessels were coagulated by bipolar coagulation and cut by micro scissors. (**D**) Little bleeding had been observed at the resection site after off-clamp partial nephrectomy. ADPJ, actuator-driven pulsed water jet. (Color version available online.)

achieve hemostasis. The size of the removed kidney in these groups was similar to that in the ADPJ group. All operations were performed by a single surgeon.

The rats were again anesthetized with isoflurane. Bladder urine and blood samples were collected, and the residual kidney was harvested at 1, 7, 14, 30, and 90 days after PN (5 rats from each group per period). These experiments were approved by the Animal Experiment Committee of Tohoku University.

Urine and Blood Samples

Postoperative renal function was evaluated by serum blood urea nitrogen (BUN) and creatinine levels (i-STAT, Abbott Point of Care, East Princeton, NJ). Urinary and serum kidney injury molecule-1 (KIM-1) levels, which are elevated in the presence of renal injury,[11,12] were measured using an ELISA kit (R&D Systems, Wiesbaden, Germany). Urinary KIM-1 levels were then adjusted by the urinary creatinine levels, measured using an ELISA kit (Trans Genic Inc., Fukuoka, Japan).

Histopathological Examination

The harvested kidneys were immediately immersed in 10% neutral buffered formalin solution. Serial 3-μm-thick sections were prepared, and their morphological features were examined in paraffin sections with hematoxylin-eosin (HE) staining. The extents of renal ischemia and oxidative stress were examined by staining for anti-1-methyladenosine (m1A), which was kindly provided by a coauthor (TA). The m1A is a transfer RNA-specific modified nucleoside that is highly sensitive to oxidative tissue damage.[13] All preparations were observed with a microscope, AxioCam MRc (Carl Zeiss Microimaging GmbH, Göttingen, Germany).

Paraffin-embedded sections were incubated for 24 h with the anti-m1A antibody (1:100) and incubated with horseradish peroxidase-labeled anti-mouse IgG (EnVision+ System— HRP, DAKO, Tokyo, Japan). Then, 3, 3'-diaminobenzidine was used for visualization, and counter-staining was performed by hematoxylin.

Quantitative Real-time Polymerase Chain Reaction

Approximately 50 mg of tissue were collected from the resection surface. Total RNA was extracted from the tissue according to the manufacturer's suggested protocol using an RNeasy Lipid Tissue Mini Kit (Qiagen GmbH, Hilden, Germany).[14] The RNA (1 μg) was converted to cDNA with an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Inc., Hercules, CA). Real-time polymerase chain reaction for each sample was performed in duplicate with a Thermal Cycler Dice Real Time System II (Takara Bio Inc., Otsu, Japan). The mRNA expression levels of glyceraldehyde-3-phospate dehydrogenase (GAPDH), as an internal control, and KIM-1 were measured. The primer sequences were GAPDH forward: 5'-CCTTCATTGACCTCCACTACATGGT-3', and reverse: 5'-CCACAACATACGTAGCACCACGATC-3'; and KIM-1 forward: 5'-TATTTGGGGGAACAGGTTGC-3', and reverse: 5'-CAAGTCACTCTGGTTAGCCGTG-3'.[15] Relative quantification of targeted gene expression was calculated using the comparative threshold cycle method.[16]

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA). All values are presented as means ± standard error. Comparisons of the 4 groups were performed using 1-way analysis of variance. A P value less than .05 was considered significant.

RESULTS

The time of off-clamp PN using the radio knife and soft coagulation were approximately 15 min, whereas that using the ADPJ system was approximately 30 min. Little bleeding had been observed at the resection site after PN using the ADPJ system (Fig. 1D). Of 100 rats, 1 had a postoperative urinoma in the soft coagulation group. No other complications or adverse events were observed during the experiments. At 90 days after surgery, the mean body weights in the Sham, ADPJ system, radio knife, and soft coagulation groups were 577 ± 17 g, 522 ± 8 g, 568 ± 24 g, and 511 ± 31 g (P = .18), respectively.

Renal Function After Off-clamp PN

Serum BUN and creatinine levels before surgery were 20.7 ± 0.9 mg/dL and 0.52 ± 0.04 mg/dL, respectively. Serum BUN levels were significantly lower in the ADPJ group than in the soft coagulation group at 1 (P < .05), 7, and 90 days (P < .01) after PN (Fig. 2A). Serum creatinine levels were also significantly lower in the ADPJ group than in the soft coagulation group at 1 (P <.05), 7 (P < .01), 14 (p < .05), and 90 days (P < .01) after PN (Fig. 2B). Although there were no significant differences, serum BUN and creatinine levels tended to be lower in the ADPJ group than in the radio knife group. On the other hand, those in the ADPJ group were similar to those in the sham group.

The urinary KIM-1 level was significantly lower in the ADPJ group than in the soft coagulation group during the experimental period (Fig. 2C). Moreover, the serum KIM-1 levels were significantly lower in the ADPJ group than in the soft coagulation group from 7 days after PN (P < .01, Fig. 2D). Although there were no significant differences, urinary and serum KIM-1 levels tended to be lower in the ADPJ group than in the radio knife group during the experimental period. There were no differences between the sham group and the ADPJ group.

Renal Damage After Off-clamp PN

HE staining of the renal tissue dissected by the ADPJ system showed crush injury and internal hemorrhage at 1 day after the operation, and this gradually recovered to be totally covered by a pseudo-membrane from 7 days after the operation. There was little thermal coagulative change of the resection surface in the ADPJ group. In contrast, broad necrosis below the resection surface was observed in almost all kidneys coagulated by the radio knife and by soft coagulation (Fig. 3A). Immunostaining with m1A, which suggested ischemia, showed that the extent of renal tissue injury was significantly smaller in the ADPJ group than in the thermal coagulation device group. In addition, the resection surfaces in the radio knife and soft coagulation groups were stained by m1A in the acute phase (Fig. 3B).

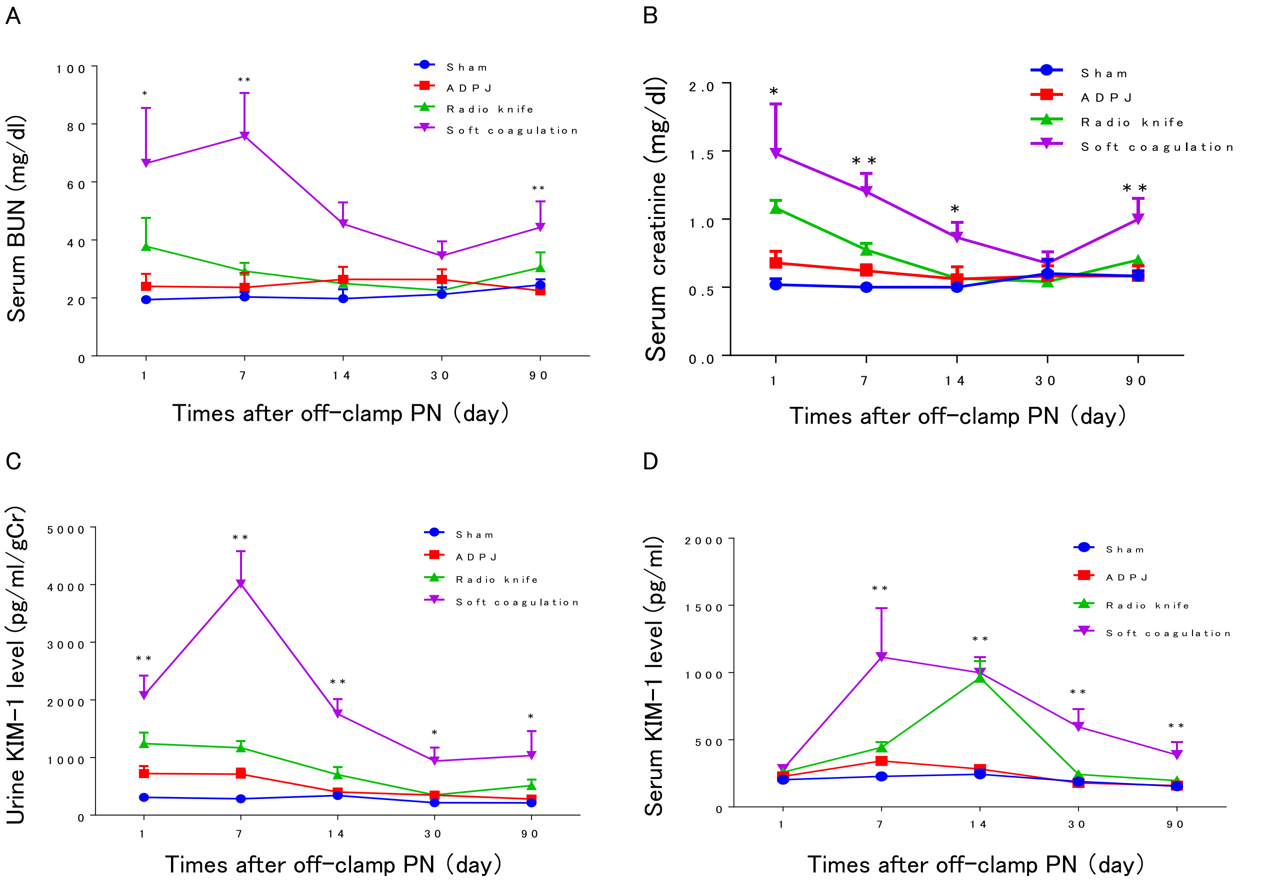

Figure 2. (**A**) Changes in serum BUN levels. Serum BUN levels after off-clamp PN are significantly lower in the ADPJ group than in the soft coagulation group at 1, 7, and 90 days after PN. (**B**) Changes in serum creatinine levels. Serum creatinine levels are significantly lower in the ADPJ group than in the soft coagulation group at 1, 7, 14, and 90 days after PN. *; $P < .05$, **; $P < .01$, (1-way ANOVA). (**C**) Changes in urinary KIM-1 levels. Urinary KIM-1 levels after off-clamp PN are significantly lower in the ADPJ group than in the soft coagulation group during the experimental period. The urinary KIM-1 level is adjusted by the urinary creatinine level. (**D**) Changes in serum KIM-1 levels. Serum KIM-1 levels after off-clamp PN are significantly lower in the ADPJ group than in the soft coagulation group from 7 days after PN. *; $P < .05$, **; $P < .01$, (1-way ANOVA). ANOVA, analysis of variance; ADPJ, actuator-driven pulsed water jet; BUN, blood urea nitrogen; KIM-1, kidney injury molecule-1; PN, partial nephrectomy. (Color version available online.)

Changes of KIM-1 Expression Levels After Off-clamp PN

Renal injury was evaluated by expressions of KIM-1 in the residual kidney. The relative expression levels of KIM-1 mRNA were determined with normalization to GAPDH, and they are presented as fold increases to normal. The expression levels of KIM-1 mRNA were significantly lower in the ADPJ group than in the soft coagulation group at 7 ($P < .01$) and 90 days ($P < .05$) after PN. Although there was no significant difference between the ADPJ and radio knife groups, the expression levels of KIM-1 mRNA tended to be lower in the ADPJ group during the experimental period (Fig. 4).

DISCUSSION

The goal of treatment for renal cell carcinoma is to improve both oncological and functional outcomes, including renal function. Many studies have shown that the amount of residual renal parenchyma after PN has a more important role in predicting postoperative renal function.[17,18] However, even though the renal parenchyma was quantitatively preserved by PN, it is unclear whether this preserved region was actually functional, since hilar clamping or sutured renorrhaphy for hemostasis might cause ischemic and necrotic changes in residual kidney.[6] Recently, off-clamp and nonsutured renorrhaphy PN procedures using soft coagulation have been reported to be safe and feasible, with little change from preoperative to postoperative renal function.[19,20] However, there is compensation by the contralateral kidney, contributing to overall renal function that might seem to be normal. In addition, although the hazards of thermal injury for postoperative renal function have not been reported, thermal coagulation might result in postoperative renal damage. Thus, the development of novel surgical devices is necessary to achieve nonhilar clamping, nonthermal dissection, and nonsutured renorrhaphy in PN.

Water jet technology based on a conventional pressure-driven continuous method[21,22] or pulsed laser[23] method

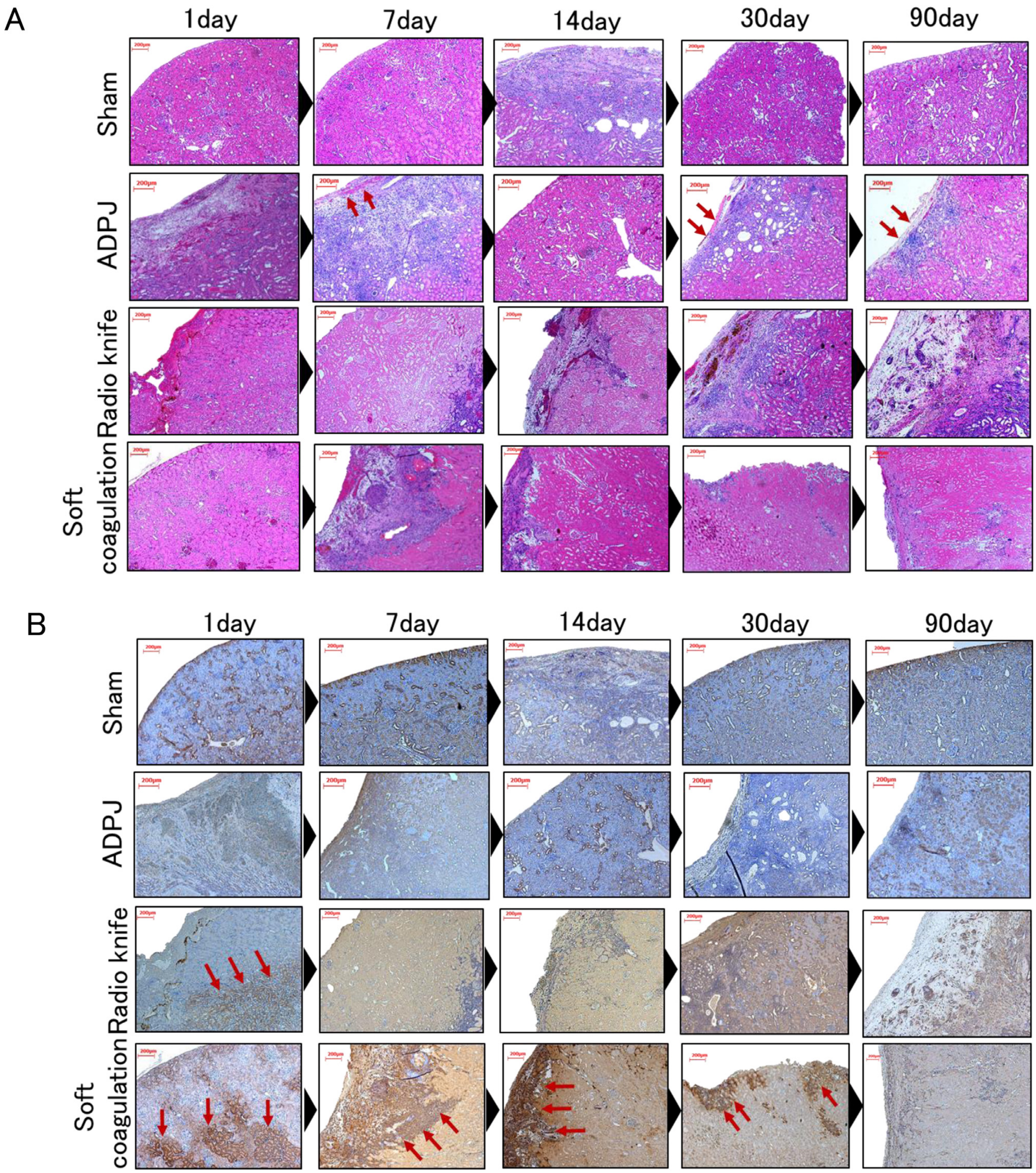

Figure 3. (**A**) Time-dependent changes in HE staining of the resection surface. HE staining of the kidney tissue dissected by the ADPJ shows crush injury and internal hemorrhage due to pressure of the nozzle tip of the resection site in the early phase, and this gradually recovers to be totally covered by a pseudo-membrane (red arrow). There is no thermal coagulative change in the resection surface following ADPJ, while a broad range of necrosis below the resection surface is observed in the resection surface coagulated by radio knife and soft coagulation. Scale bar indicates 200 μm. (**B**) Time-dependent changes in immunohistochemical staining of the resection surface. Immunostaining with m1A is significantly less in the ADPJ group than in the thermal coagulation device group. The red arrow shows the resection surfaces following radio knife and soft coagulation stained by m1A in the acute phase, but then the background of the hematoxylin disappears, suggesting that the area has developed extensive necrosis. Scale bar indicates 200 μm. HE, hematoxylin-eosin. (Color version available online.)

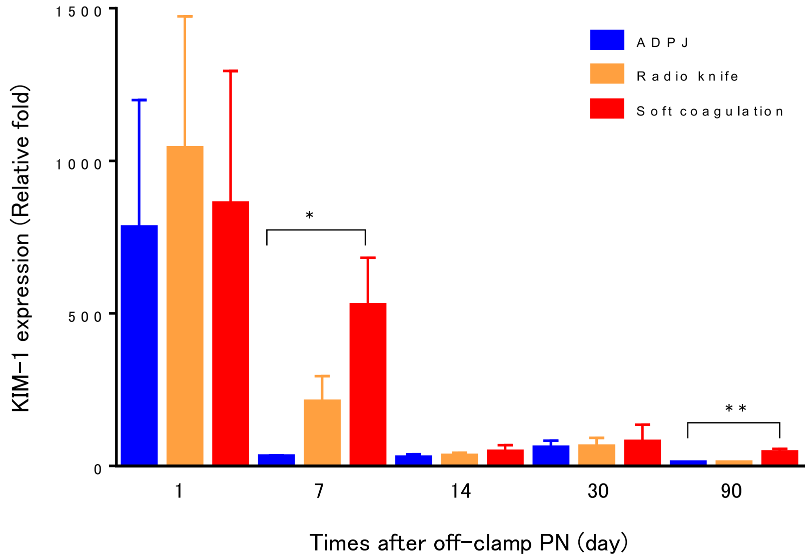

Figure 4. Expressions of KIM-1 in the residual kidney after off-clamp PN. The relative quantification expresses fold differences in KIM-1 expression between groups, normalized to GAPDH and relative to the normal renal tissue. The value obtained with the normal renal tissue was used as one arbitrary unit. The expressions of KIM-1 were elevated in the radio knife and soft coagulation groups compared with the ADPJ group in each term. Especially, KIM-1 expressions were significantly lower in the ADPJ group than in the soft coagulation group at 7 (*; $P < .01$) and 90 days (**; $P < .05$) after PN. GAPDH, glyceraldehyde-3-phospate dehydrogenase; KIM-1, kidney injury molecule-1; PN, partial nephrectomy. (Color version available online.)

provides promising results in terms of dissecting tissue. It can selectively dissect tissue with preservation of fine blood vessels (approximately 100-200 μm) and nerves, based on the different tensile strengths of tissues against the jet flow.[21] Therefore, water jet technology has been commonly used to reduce blood loss and parenchymal trauma in liver surgery compared to ultrasonic aspiration or blunt dissection, because the liver contains an abundant small vessel network.[24] In regard to off-clamp PN using hydro-jet technology was performed in an animal experiment and a clinical trial, and its technical feasibility and minimal traumatic parenchymal changes were confirmed.[25,26] Another advantage of this technology is the absence of the thermal damage that is inevitable with other commercially available instruments. Recently, a piezoelectric actuator has been developed to replace a pulsed laser system, and we have developed a piezo ADPJ system that can dissect tissues while preserving fine blood vessels and causing no thermal injury.[8] Importantly, the ADPJ system is clearly different from a conventional water jet dissector, since the ADPJ system offers an intermittent water flow, providing a greater opportunity for precise dissection within a certain depth and less water volume than a conventional continuous water jet. Seto et al reported that the dissection characteristics of pulsed jets were superior to those of existing continuous water flows in a basic engineering experiment.[8] This ADPJ system might solve the problems of conventional PN.

Regarding renal function after off-clamp PN using the ADPJ system, serum BUN, and creatinine were not increased within 90 days. The urinary and serum KIM-1 levels, biomarkers of renal injury, were also markedly lower in the ADPJ group than in the soft coagulation group. In addition, KIM-1 mRNA expression of the resection surface was obviously decreased in the ADPJ group. These results suggested that the ADPJ system might show no effect of thermal injury on split renal function, compared with other thermal coagulation devices.

Yamada et al reported that hepatectomy using the ADPJ system resulted in histologically less injury than the existing radio knife and a supersonic wave aspirator in swine.[27] In the present study, the resection surface with the ADPJ system was less injured than with thermal coagulation devices on HE staining. Interestingly, recovery after dissection using the ADPJ system was different from that by the other thermal coagulation devices, with good wound healing. Furthermore, m1A immunostaining showed that the m1A expressions were strong in the acute phase with thermal coagulation devices, while the expression was weak in the ADPJ group, leading to less tissue injury. Thus, the ADPJ system could attenuate renal damage after off-clamp PN.

Clamping time of the hilus or sutured renorrhaphy has been suggested as a predictor of renal ischemia after PN,[6] whereas thermal injury should be considered a risk factor for renal damage. In the present study, 1 surgeon performed all off-clamp PNs under the same conditions, so the differences in renal function and damage in the resection surface might be related to the characteristics of each surgical device. The ADPJ system could minimize renal damage after off-clamp PN compared to the conventional surgical devices, contributing to the prevention of postoperative CKD.

Moreover, we have reported that the breaking strength of human kidney was obviously different between the pseudo tumor capsule and renal parenchyma.[10] If the

ADPJ voltage were set to the same intensity of renal parenchyma, the ADPJ system might dissect the renal parenchyma safely, without injuring the pseudo tumor capsule. Thus, the ADPJ system might be a useful surgical device in PN for renal cell carcinoma with a pseudo tumor capsule, which safely achieves nonhilar clamping, nonthermal dissection, and nonsutured renorrhaphy.

There are several limitations in the present study. First, there were no significant differences between the ADPJ and radio knife groups in urine and blood sample test results. However, histologically, differences were observed between the ADPJ group and radio knife group. The renal damage by the radio knife might be underestimated because the vessels in the rat kidney were small and could be easily controlled for a few seconds by the radio knife. Also, the time of PN using the ADPJ system was longer than that of using the radio knife or soft coagulation, since preserved fine blood vessels using the ADPJ system were coagulated by bipolar coagulation and cut by micro scissors in the ADPJ group. The ADPJ system, such as equipped with a bipolar function, should be developed to shorten the dissection time for the clinical trials in human. Second, the impact of sutured renorrhaphy on the postoperative renal damage had not been evaluated in the present study, because this study focused on the postoperative damage of residual kidney with each surgical device in itself. However, the sutured renorrhaphy was reported to influence postoperative renal function,[6] and it is necessary to examine the influence of sutured renorrhaphy in a future study. Finally, the experimental period was 90 days after PN. This period was not very long, but the serum BUN and KIM-1 levels in the ADPJ group were similar to those in the sham group at 90 days after PN. We previously reported that off-clamp laparoscopic PN using the ADPJ system could be performed safely in swine,[10] but the long-term outcomes were not evaluated. Thus, it is necessary to clarify the long-term outcomes after PN using a more robust model such as swine in a further experiment for the clinical trials in human.

In conclusion, the piezo ADPJ system resulted in less renal damage after off-clamp PN than existing thermal coagulation devices, contributing to decreased postoperative CKD.

CONFLICT OF INTEREST

AN and TT received research support for this study from Seiko Epson Co., Ltd. under a collaborative research contract with Tohoku University.

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References

1. Pichler M, Hutterer GC, Chromecki TF, et al. Renal cell carcinoma stage migration in a single European centre over 25 years: effects on 5- and 10-year metastasis-free survival. *Int Urol Nephrol*. 2012;44:997–1004.
2. Sugimoto K, Shimizu N, Nose K, et al. Clinical outcome of small renal cell carcinoma after delayed surgery versus immediate surgery. *J Cancer*. 2013;19:514–518.
3. Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol*. 2009;182:1271–1279.
4. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015;67:913–924.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
6. Mir MC, Pavan N, Parekh DJ. Current paradigm for ischemia in kidney surgery. *J Urol*. 2016;195:1655–1663.
7. Kaczmarek BF, Tanagho YS, Hillyer SP, et al. Off-clamp robot-assisted partial nephrectomy preserves renal function: a multi-institutional propensity score analysis. *Eur Urol*. 2013;64:988–993.
8. Seto T, Yamamoto H, Takayama K, Nakagawa A, Tominaga T. Characteristics of an actuator-driven pulsed water jet generator to dissecting soft tissue. *Rev Sci Instrum*. 2011;82 055105.
9. Yamashita S, Kamiyama Y, Nakagawa A, Kaiho Y, Tominaga T, Arai Y. Novel pulsed water jet system permits off-clamp partial nephrectomy in swine. *Int J Urol*. 2014;21:1181–1182.
10. Kamiyama Y, Yamashita S, Nakagawa A, et al. The piezo actuator-driven pulsed water jet system for minimizing renal damage after off-clamp laparoscopic partial nephrectomy. *Tohoku J Exp Med*. 2017;243:57–65.
11. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int*. 2002;62:237–244.
12. McIlroy DR, Wagener G, Lee HT. Biomarkers of acute kidney injury: an evolving domain. *Anesthesiology*. 2010;112:998–1004.
13. Mishima E, Inoue C, Saigusa D, et al. Conformational change in transfer RNA is an early indicator of acute cellular damage. *J Am Soc Nephrol*. 2014;10:2316–2326.
14. Mongroo PS, Johnstone CN, Naruszewicz I. Beta-parvin inhibits integrin-linked kinase signaling and is downregulated in breast cancer. *Oncogene*. 2004;23:8959–8970.
15. Ajay AK, Kim TM, Ramirez-Gonzalez V, Park PJ, Frank DA, Vaidya VS. A bioinformatics approach identifies signal transducer and activator of transcription-3 and checkpoint kinase 1 as upstream regulators of kidney injury molecule-1 after kidney injury. *J Am Soc Nephrol*. 2014;25:105–118.
16. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods*. 2001;25:402–408.
17. Liss MA, DeConde R, Caovan M, et al. Parenchymal volumetric assessment as a predictive tool to determine renal function benefit of nephron-sparing surgery compared with radical nephrectomy. *J Endourol*. 2016;30:114–121.
18. Kotamarti S, Rothberg MB, Danzig MR, et al. Increasing volume of non-neoplastic parenchyma in partial nephrectomy specimens is associated with chronic kidney disease upstaging. *Clin Genitourin Cancer*. 2015;13:239–243.
19. Ota T, Komori H, Rii J, et al. Soft coagulation in partial nephrectomy without renorrhaphy: feasibility of a new technique and early outcomes. *Int J Urol*. 2014;21:244–247.
20. Hongo F, Kawauchi A, Ueda T, et al. Laparoscopic off-clamp partial nephrectomy using soft coagulation. *Int J Urol*. 2015;22:731–734.
21. Oertel J, Gaab MR, Knapp A, Essig H, Warzok R, Piek J. Water jet dissection in neurosurgery: experimental results in the porcine cadaveric brain. *Neurosurgery*. 2003;52:153–159.
22. Oertel J, Gaab MR, Pillich DT, Schroeder HW, Warzok R, Piek J. Comparison of waterjet dissection and ultrasonic aspiration: an in vivo study in the rabbit brain. *J Neurosurg*. 2004;100:498–504.

23. Hirano T, Komatsu M, Saeki T, et al. Enhancement of fibrinolytics with a laser-induced liquid jet. *Lasers Surg Med*. 2001;29:360–368.
24. Rau HG, Duessel AP, Wurzbacher S. The use of water-jet dissection in open and laparoscopic liver resection. *HPB (Oxford)*. 2008;10:275–280.
25. Basting RF, Djakovic N, Widmann P. Use of water jet resection in organ-sparing kidney surgery. *J Endourol*. 2000;14:501–505.
26. Moinzadeh A, Hasan W, Spaliviero M, et al. Water jet assisted laparoscopic partial nephrectomy without hilar clamping in the calf model. *J Urol*. 2005;174:317–321.
27. Yamada M, Nakano T, Sato C, et al. The dissection profile and mechanism of tissue-selective dissection of the piezo actuator-driven pulsed water jet as a surgical instrument: laboratory investigation using swine liver. *Eur Surg Res*. 2014;53:61–72.