Hemostatic Effect of New Surgical Glue in Animal Partial Nephrectomy Models

Yasuyuki Naitoh, Akihiro Kawauchi, Kazumi Kamoi, Jintetsu Soh, Koji Okihara, Suong-Hyu Hyon, and Tsuneharu Miki

OBJECTIVE To evaluate the hemostatic effect of newly developed medical adhesive in animal partial nephrectomy models.

MATERIALS AND METHODS A total of 30 experimental rabbits were used in the first study. After clamping the renal vessels, partial nephrectomy was performed up to the opening of the calices. Bioglue was applied to the resection stumps using the new glue (group 1, n = 10) or fibrin glue (group 2, n = 10) for 2 minutes, and the blood loss was measured after unclamping the vessels. Simple unclamping without glue (group 3, n = 10) was also evaluated. For the second study, we used 9 dogs with blood pressure monitoring. After preparation similar to that for the first study, the new glue was applied in 3 dogs (group 4), fibrin glue in 3 dogs (group 5) and no glue in 3 dogs (group 6). Histologic evaluation was performed at 7 days and 1 month after surgery.

RESULTS The mean blood loss was significantly less in group 1 (1.45 g) than in groups 2 (6.59 g) and 3 (19.77 g; $P < .001$ for both). It was also significantly less in group 4 (12.5 g) than in group 5 (182.5 g; $P < .001$). Group 4 maintained their initial blood pressure throughout the study, but a significant decrease was observed in group 5. No hematoma was observed at day 7.

CONCLUSION The new glue showed acceptable hemostasis when applied to the resection stumps after partial nephrectomy in both the rabbit and the dog models. These findings indicate that it could be useful for hemostasis after partial nephrectomy. UROLOGY 81: 1095–1100, 2013. © 2013 Elsevier Inc.

Laparoscopic partial nephrectomy (LPN) has been recognized as a standard procedure to treat patients with small renal tumors.[1-5] In LPN for small renal cell carcinoma, hemostatic control at the resection stump is highly critical.[6,7] The medical tissue adhesives currently used in clinical practice include cyanoacrylate glues, fibrin glue, and so forth.[8-11] However, in practice, a single application of these adhesives has not been sufficient to control hemorrhaging at the resection stump owing to the weak adhesiveness of the products, which have served more as an adhesive aid. Furthermore, these adhesives have the various problems associated with blood derivatives, such as the possibility of infection, issues of degradability in vivo, safety, and cost.

We have developed a new glue, a novel medical adhesive, using food additives. The advantages of this adhesive include the lack of a risk of infection, superior self-degradability, and low cost. Once this tissue adhesive has been proved to be highly effective and safe in controlling hemostasis at the resection stump during LPN, with a single application, it will be extremely useful. In the present study, we performed animal experiments to evaluate the efficacy of this new glue during LPN.

MATERIAL AND METHODS

Development of New Surgical Glue

The new glue is composed of a Schiff base formation of aldehyde dextran and ε-poly(L-lysine). In brief, 20 g of dextran (70 KDa, Meito Sangyo, Aichi, Japan) was dissolved in 80 mL of distilled water; 3 g of sodium periodate dissolved in 40 mL of water was added to the dextran solution. The oxidation reaction proceeded at 50°C for 1 hour, followed by dialysis and air drying. To control the time of gelation and degradation, 0.5 g of succinic anhydride was added to 20 g of aqueous ε-poly(L-lysine) (25 wt/wt%, 4 KDa, Chisso, Tokyo, Japan) and stirred at 50°C for 1 hour to partially acylate the amino goups in ε-poly(L-lysine). Through the process of air drying, ε-poly(L-lysine) with 12 mol% of acylation was recovered. Next, 10 g of aldehyde dextran (-CHO content 0.30/sugar unit) and 2.5 g of ε-poly(L-lysine) were mixed and crushed into a fine powder with particles <0.1 mm in diameter. This powder can be immediately gelled by the addition of a small amount of water.

Both aldehyde dextran and ε-poly(L-lysine) are food additives and not derived from a biologic source. A unique glue-spraying device we have developed was used in the present study.

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; and Center for Fiber and Textile Science, Kyoto Institute of Technology, Kyoto, Japan

Reprint requests: Akihiro Kawauchi, M.D., Ph.D., Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kyoto 602-8566, Japan. E-mail: kawauchi@koto.kpu-m.ac.jp

Submitted: November 27, 2012, accepted (with revisions): January 2, 2013

http://dx.doi.org/10.1016/j.urology.2013.01.002

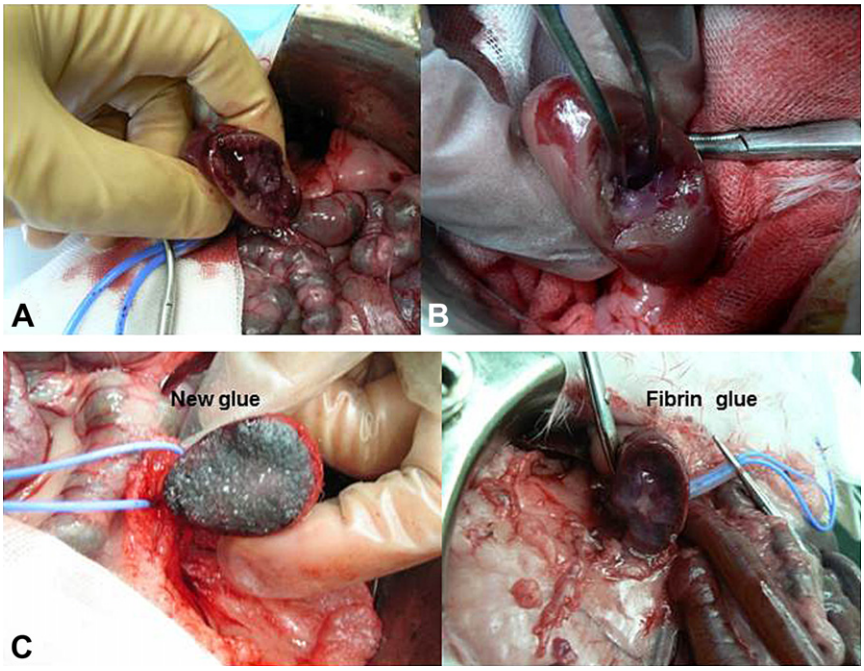

Figure 1. **(A)** Partial resection stump created as large as possible. **(B)** Renal pelvis opened in each case. **(C)** Glue dispersed after clamping renal blood vessels.

Hemostatic Effect of New Surgical Glue

The animal experimentation committee of our university approved the experiments. All surgical and euthanasia treatments were performed in accordance with the National Institutes of Health animal care guidelines.

Partial Nephrectomy Using Experimental Rabbits. Experimental rabbits (mean body weight approximately 4 kg) were used in the first animal model. Ketamine hydrochloride was intramuscularly injected at 15 mg/kg body weight. After the experiment, penicillin G was intramuscularly injected at 20,000 U/kg body weight.

The rabbits were placed in the supine position, and the abdominal cavity was opened. The kidney was fixed, and the renal vessels were clamped. To increase the sectioned renal area, the outer side of the kidney was excised obliquely. In all experiments, the section sizes were adjusted to be equal. It was confirmed that the renal calices remained open to evaluate urine leakage (Fig. 1A,B).

For hemostasis, the resection stump was covered with the new glue (n = 10), commercially available fibrin glue (n = 10), or left without glue (n = 10). The fibrin glue was used in the present study as a control (Fig. 1C). The fibrin glue consisted of 2 components. Solution 1 is a protein concentrate consisting of fibrinogen, plasma fibronectin, factor VIII, and plasminogen, reconstituted in an aprotinin solution. Solution 2 is thrombin reconstituted in a calcium chloride solution. Both solutions were sprayed onto the resection stump. At 2 minutes after the completion of hemostatic treatment, the renal vessels were unclamped, and the blood loss was measured for 7 minutes.

The resected stumps were evaluated macroscopically and histologically at 7 days and 1 month after surgery. The whole kidney was immersed with 10% formalin. After fixation, each resection stump was resected, embedded in paraffin, sectioned, and subjected to hematoxylin-eosin staining.

Partial Nephrectomy Using Experimental Dogs With Blood Pressure Monitoring. The second experiment was performed to evaluate the hemostatic effect of the treatment in dogs (mean body weight 10 kg) with blood pressure monitoring.

The dogs were anesthetized by an intramuscular injection of ketamine hydrochloride at 15 mg/kg and xylazine at 7 mg/kg. After intratracheal intubation, mechanical ventilation was started (50% oxygen, 50% nitrous oxide mixed with 1% halothane) to allow maintenance of anesthesia by inhalation during treatment. After the experiment, penicillin G was intramuscularly injected at 20,000 U/kg body weight.

After securing hemostasis by applying the adhesive, the kidneys were reperfused, and the amount of blood loss from the resection stump was measured. During the experiment, the blood pressure of the femoral artery was also recorded.

Hemostasis was performed using the new glue (n = 3), fibrin glue (n = 3) or glue (n = 3). The experimental procedures were the same as those used for the rabbit study. The resected stumps were evaluated macroscopically and histologically at 7 days and 1 month after surgery.

Carcinogenic Potential

The carcinogenic potential of the new glue in rabbits was also evaluated. A gross examination and histopathologic evaluation were performed 2 years after treatment.

RESULTS

Hemostatic Effect of New Glue

Partial Nephrectomy Using Experimental Rabbits. Hemostasis was achieved within 7 minutes in the new glue group and fibrin glue group. The mean blood loss was 1.45 g in the new glue group, 6.59 g in the fibrin glue