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Abbreviations: FDA, US Food and Drug Administration; UC, urothelial cancer.

Fibrin gel-assisted stone extraction in retrograde intrarenal surgery

Small stone fragments inevitably result from breakage of a large stone and are almost impossible to be entirely extracted from the collecting system in current retrograde intrarenal surgery (RIRS) settings. While most of these clinically insignificant residual fragments (CIRFs; <4 mm) may pass spontaneously, increasing evidence suggests that these so-called CIRFs may act as an origin for new stone formation and eventually lead to re-intervention [1]. Therefore, it is of paramount importance to achieve complete stone-free status with the aim of improving patient's quality of life not only physically but also psychologically and economically [2]. In the present study, we present an effective technique using a fibrin-based gel to clear out small stone fragments from the collecting system during RIRS. The fibrin-based gel used in this study was a self-modified version of a commercially available product that has already been widely used for haemostasis and wound sealing in various clinical settings. The original gel system includes two components: component A (main constitutes: fibrinogen and various fibrin stabilisers) and component B (thrombin and Ca^{2+}). When diluted appropriately and supplemented with medical grade methylene blue, the two components form a blue fibrin gel that embeds and adheres stone fragments in the saline and urine environment within seconds after sufficient mixing. The fibrin gel-assisted stone extraction technique does not require any specific instruments other than standard RIRS requirements and serves as an 'additional procedure' that does not change the protocol of standard RIRS lithotripsy. This technique might fuel the growing popularity and expanding indication of RIRS in the treatment of upper tract stones, by reducing the risk of leaving behind CIRFs that can sometimes be clinically significant.

Patients bearing a single 10–30 mm upper tract stone without RIRS contradictions were enrolled in this study between February 2021 and July 2021. Patients were not routinely stented before surgery. Ureteric stents were placed in all patients on the affected side and routinely removed 2 weeks after RIRS. All patients were followed up for a minimum of 1 month (range 1–6 months).

Surgical Techniques

All surgeries were performed by a single RIRS surgery team. A 12-F ureteric access sheath (UAS) was used in all cases.

1. Patient preparation, patient positioning, rigid ureteroscopy and UAS placement. Same as standard RIRS protocol.
2. Stone transposition, fragmentation, pop-dusting and stone extraction without gel. Target stones are placed in a suitable upper or middle calyx by basketing (Fig. 1A). Ideally, stone fragmentation and pop-dusting are performed until all stones are dusted to <2 mm (Fig. 1B). The basket can be used to retrieve larger fragments that cannot be efficiently dusted.
3. Prepare gel-injection device. Establish gel-injection device with two or three three-way connecters that are connected to three 20-mL syringes loaded with gel component A, gel component B, and saline, respectively (Fig. 1C).
4. Gel injection and extraction. After ensuring sufficient dusting by checking all calyxes, calyxes filled with stone fragments are noted and the gel-injection route planned. Move the flexible ureteroscope (fUS) tip close to the sedimented stone fragments and simultaneously inject an appropriate amount of both gel components quickly enough to blow up the sedimented fragments through the 3-F fUS working channel. The two components should solidify to form a blue, semi-transparent, and semi-rigid gel that embeds and adheres stone fragments within seconds. Follow the planned route and find the next calyx sedimented with stone fragments and perform gel injection until all designated calyxes are filled with gel (Fig. 1D). Inject ≥2 mL saline to flush out residual components in the fUS working channel. A guidewire can easily clear the channel completely in case of blockage. Check the formation and location of the gel-

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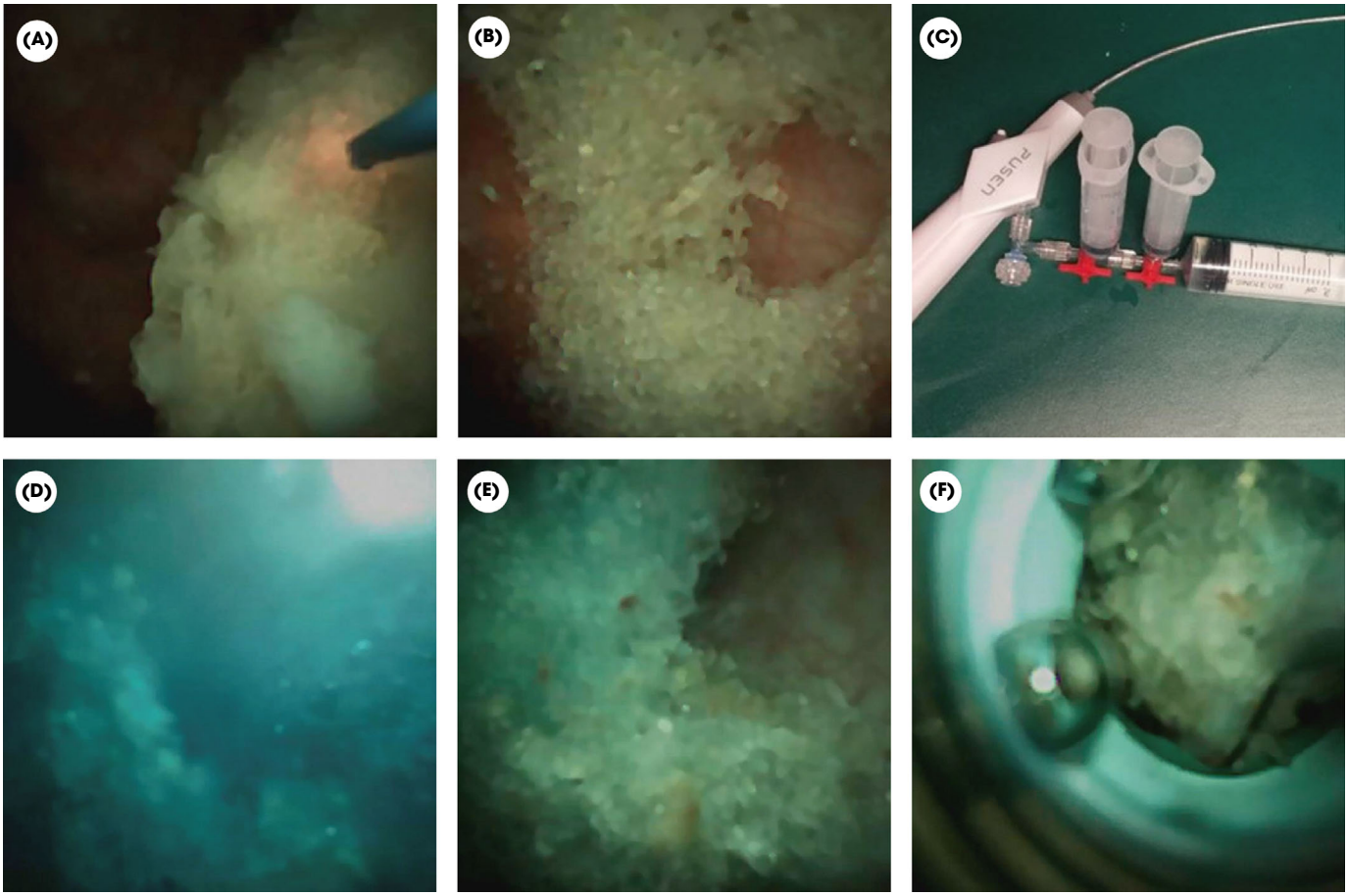
Fig. 1 Fibrin gel-assisted RIRS lithotripsy. (**A**) fragmentation and pop-dusting. (**B**) Confirm sufficient dusting, locate fragments-sedimented calyxes and plan gel injection route. (**C**) A simple gel-injection device consists of two three-way connecters and three syringes loaded with the two gel components and saline separately. (**D**) Gel injection. (**E**) Check and locate gel-stone complex. (**F**) Basket extraction of gel-stone complex.



stone complex after removing the gel-injection device and re-establish irrigation (Fig. 1E). Use the basket to extract the gel-stone complex piece by piece until the blue-dyed gel is completely absent in the collecting system (Fig. 1F). Repeat the gel injection and extraction cycle until a satisfactory stone clearance rate (SCR) is achieved.

A total of 55 patients (26 female) bearing a single 10.0–30.0 mm upper tract stone with no RIRS contradictions were administered and enrolled in this study. The mean (SEM, range) patient age was 49.1 (12.6, 20–82) years. The mean (SEM, range) largest stone size was 15.3 (4.8, 10.0–30.0) mm, stone volume was 1683.1 (1674.1, 332.8–8386.6) mm^3 (stone volume = 0.52 × long axis × short $axis^2$), and the average stone density was 1036.5 (259.1, 211.0–1601.0).

The mean (SEM, range) total fUS time was 56.2 (22.1, 32.0–129.0) min. The mean (SEM, range) time for basket extraction was 29.9 (15.3, 10.0–70.0) min. A mean (SEM, range) of 2.7 (0.7, 2–5) cycles of gel injection and extraction were performed in each patient.

Non-contrast CT (NCCT) was performed on the first day after surgery to determine surgical clearance of stones. The results showed that the mean (SEM, range) largest residual stone was 0.9 (1.2, 0–4.0) mm and residual stone volume was 3.1 (7.0, 0–33.3) mm^3 (residual stone volume = 0.52 × long $axis^3$). Complete absence of any stone fragments was noted in 31 patients, yielding a complete stone-free rate (SFR) of 56.4% (SFR = No. of complete stone free patientsNo. of total patients×100%). Incorporating the original stone volume assessed by preoperative NCCT, the mean (SEM, range) SCR was calculated as 99.9 (0.3, 98.3–100.0)% (SCR = 1-residual stone volumepreoperative stone volume×100%). Five of the 55 patients had fever and were managed conservatively with conventional antibiotic treatment. No other complication was noted.

Current RIRS lithotripsy techniques and instruments sometimes inevitably yield numerous small stone fragments.

Efforts have been made with the aim of eliminating these small stone fragments by using different types of stone baskets, modifications of flushing instruments and techniques [3], and modifications of patient positioning [4], etc. Unfortunately, complete clearance of small stone fragments of ≤2 mm remains a challenge. In this study, we propose an effective strategy of using fibrin gel to retrieve small stone fragments during RIRS lithotripsy. Similar ideas of using stone adhesives have been previously reported in open pyelolithotomy that used autologous blood as a stone adhesive [5] and in an *in vivo* porcine kidney RIRS model that used a patented artificially synthesised polysaccharide-based stone adhesive that required a specific solubiliser to be cleared from the collecting system [6].

Fibrinogen enzymatically forms fibrin monomer mediated by thrombin and various fibrin stabilisation factors, which covalently bind to each other to form a stable fibrin network [7]. The liquid portion in solidified fibrin 'gel' can be squeezed out, leaving a small proteinaceous clot with great elasticity and tensile strength. The physical properties of fibrin gel, or 'net', explains why it adheres to and embeds stone fragments, and can 'shape-shift' and be extracted by basket through the UAS. Although there were few residual stones following gel-assisted RIRS (SCR of 99.9%), this occurred in less than half of the cases (SFR of 56.4%). Residual stones were those free-floating fragments that did not adhere to or embed in the gel. Therefore, the gel should not risk making residual fragments more difficult to be passed, as long as the gel is completely removed. More importantly, the fibrin gel spontaneously dissolves in human urine gradually when incubated in a 37 °C water bath as we bench tested (data not shown). Although residual fibrin gel was not encountered in any of our cases, as the blue-dyed gel was readily identifiable and did not tend to adhere to mucosa, future investigation targeting faster gel dissolving is required to completely obviate the risk of residual gel causing obstruction or other problems. Last but not least, further comparative studies are required to elucidate the exact advantage of gel assistance and possible drawbacks, e.g. whether extended operation time leads to a higher complication rate or not.

Using fibrin gel to adhere and embed small stone fragments followed by subsequent extraction via a stone basket appeared to be an effective technique for achieving complete stone clearance. Although our initial experience suggests that a satisfactory SCR can be achieved within an acceptable operation time, further studies are required to establish the role of this technique in endoscopic lithotripsy.

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Disclosure of Interest

All authors claimed no conflict of interests stated in the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Ethical Approval

A patient consent form with guarantees of confidentiality and a brief description of the techniques and costs was provided to and signed by each patient before surgery. The present study was approved by Ethics Committee of the First Affiliated Hospital of Nanchang University (internal Institutional Review Board-approved protocol number: 2020-007). In lieu of a formal ethics committee, this study followed the principles of the Helsinki Declaration.

Author Contributions

Conception and design: Xiaochen Zhou and Renrui Kuang. Surgeons: Renrui Kuang and Xiaochen Zhou. Acquisition of data: Yue Yu, Yujun Chen, Jun Deng, Jieping Hu, Mengzhen Wang, Wei Liu, Xiaoqiang Liu, Longhui Lin and Chen Li. Analysis and interpretation of data: Xiaochen Zhou, Yue Yu and Yujun Chen. Drafting of the manuscript and statistical analysis: Xiaochen Zhou and Yujun Chen. Critical revision: Gongxian Wang, Bin Fu and Haibo Xi. Obtaining funding: Xiaochen Zhou.

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Abbreviations: CIRFs, clinically insignificant residual fragments; fUS, flexible ureteroscope; NCCT, non-contrast CT; RIRS, retrograde intrarenal surgery; SCR, stone clearance rate; SFR, stone-free rate; UAS, ureteric access sheath.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. A video of the procedure. Available at: https://www.dropbox.com/s/9dh7k0rbxr6vpzg/wetransfer_.