Is hemostatic agent effective and safe in minimally invasive partial nephrectomy?

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To the Editor: Renal cell carcinoma (RCC) is one of the top ten most common cancers in adults.[1] Partial nephrectomy (PN) is the standard treatment for small RCC.[2] In recent decades, minimally invasive PN, including robotic-assisted partial nephrectomy (RAPN) and laparoscopic partial nephrectomy (LPN), has been considered as a viable alternative for open PN due to its less invasive approach. As a result, shorter hospital stay and favorable clinical outcomes are observed in RCC patients after minimally invasive PN treatment.[2] Intraoperative or post-operative hemorrhage and urinary leakage (UL) are the most common post-operative complications after PN, with the incidence rates of 1.2% to 9.5% and 1.2% to 4.5%, respectively.[3] Given that it is difficult to identify the complex renal vascularity and vascular border, one of the biggest challenges during minimally invasive PN is to minimize blood loss in the operating field.[3] At present, suture is recognized as the standard hemostatic method in PN for archiving renal parenchymal hemostasis.[3] To improve hemostasis and reduce the incidence of surgical complications after PN, a wide variety of hemostatic agents (HAs) have been developed and implemented. Topical biodegradable HAs, such as fibrin sealants (eg, TachoSil® [Takeda Pharma A/S, Linz, Austria], Tisseel® [Baxter Healthcare Corp., Deerfield, IL, USA], and Evicel® [OMRIX Biopharmaceuticals Ltd, Ramat Gan, Israel]), gelatin matrix thrombin sealants (eg, FloSeal® [Baxter Healthcare Corp., Deerfield, IL, USA]), etc, are the best choice owing to their low toxicity and natural degradation.[4]

A survey showed that HA was effectively used in 75.6% and 80.9% of patients who underwent LPN and RAPN, respectively.[5] HA was often combined with suture (hereinafter referred to as additional HA) to achieve hemostasis in clinical practice. A survey of 570 cases found that the use of HA was combined with suture in 80.3% of cases.[5] However, there is no clear evidence to support the use of additional HA in PN. Therefore, this study aimed to systematically review the existing studies reporting the effects of additional HA plus suture *vs.* suture alone on post-operative complications and hemostasis after minimally invasive PN.

A comprehensive literature search was conducted using the PubMed, Ovid EMBASE, CENTRAL, and Clinical Trials. gov databases to obtain related studies from inception to June 30, 2021. Detailed search strategies are shown in Supplementary Appendix 1, http://links.lww.com/CM9/A938.

The inclusion criteria for this meta-analysis were: (1) patients diagnosed with RCC and having undergone minimally invasive PN; (2) intervention: additional HA plus suture *vs.* suture alone; and (3) study design:

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randomized controlled trials (RCTs) or cohort studies. The primary outcomes included blood transfusion rate BTR), UL, and "hemorrhagic complications (HCs)". HCs were defined as the rates of postoperative bleeding (not requiring blood transfusion), pseudoaneurysm, arteriovenous fistula, hematoma, and hematuria. The secondary outcomes included length of stay (LOS), estimated blood loss (EBL), warm ischemia time (WIT), and operative time (OT).

Studies were excluded according to the following criteria: (1) renal tumors with lymph node and venous involvement; (2) studies including patients who underwent open PN; (3) HA alone *vs*. suture alone, or additional HA plus suture *vs*. HA alone; (4) only conference abstracts; (5) different interventions performed in the same group; and (6) duplicate publication.

After removing duplicate studies, two independent reviewers screened all titles and abstracts, and then reviewed the full text of related records. Disagreements were resolved by reaching a consensus after discussion. The following data were extracted independently by two reviewers: study characteristics (eg, first author, country, year of publication, study design, follow-up duration, and HA application), patient demographics (eg, age, gender ratio, sample size, surgical procedures, and tumor size), and perioperative outcomes. The extracted data were subsequently cross-checked by a third reviewer.

Risk-of-bias assessment was carried out by two independent reviewers according to the Newcastle–Ottawa scale for cohort studies. Any discrepancies were resolved by consulting a third experienced reviewer. The quality of studies with 8 or 9 stars was regarded as high, 6 or 7 stars was moderate, and $\leq$5 stars was low.

Means and standard deviations (SDs), or counts and percentages of occurrences, were extracted from each study. If the included studies did not report exact means and SDs, data conversion and merging were performed to obtain the estimated values using the formula recommended by Cochrane. For continuous variables, the inverse variance model was used to calculate the mean difference (MD) and 95% confidence interval (CI), whereas the odds ratio (OR) with 95% CI was estimated for dichotomous outcomes.

Heterogeneity was examined using the chi-square test ($P < 0.1$) and I^2 statistics (50%). If no significant heterogeneity ($P > 0.1$ or $I^2 < 50\%$) was found, the pooled effect was calculated using the fixed-effects model; otherwise, the random-effects model was applied. The interpretation of I^2 according to Professor Julian Higgins' theory was as follows: might not be important heterogeneity ($0\% < I^2 < 40\%$), moderate heterogeneity ($30\% < I^2 < 60\%$), substantial heterogeneity ($50\% < I^2 < 90\%$), and considerable heterogeneity ($75\% < I^2 < 100\%$). Subgroup analyses were carried out to assess the impact of different surgical procedures of PN (RAPN and LPN) and HA types (fibrin sealant and gelatin matrix thrombin sealant). Publication bias was evaluated using the Egger's test and funnel plots. All statistical tests were performed with Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK) and STATA version 14 (StataCorp, College Station, TX, USA). The threshold for statistical significancewas set to two-sided α of 0.05.

A total of ten studies involving 1976 patients were included [Supplementary Appendix 2, http://links.lww.com/CM9/A938]. Seven and three studies were related to LPN and RAPN, respectively. The results of methodological quality assessment with Newcastle–Ottawa Scale showed that the quality of six studies (6/10) was high, while that of four studies (4/10) was moderate [Supplementary Appendix 3, http://links.lww.com/CM9/A938].

The results of meta-analysis showed that there were no significant differences in BTR, UL, HCs, LOS, EBL, WIT, and OT between the additional HA plus suture groups [Supplementary Appendix 4, http://links.lww.com/CM9/A938].

The subgroup analyses of different surgical procedures of PN revealed that additional HA could significantly reduce the rates of UL (OR = 0.26, 95% CI = 0.09–0.78, $P = 0.02$) and HCs (OR = 0.25, 95% CI = 0.07–0.90, $P = 0.03$) in LPN, but there were no significant differences in BTR, UL, and HCs between the additional HA plus suture groups during RAPN. Besides, the use of additional HA did not significantly improve LOS, EBL, WIT, and OT after LPN or RAPN [Supplementary Appendix 5, http://links.lww.com/CM9/A938].

The subgroup analyses of different HA types demonstrated that there was a lower rate of HCs (OR = 0.40, 95% CI = 0.17–0.96, $P = 0.04$) in the fibrin sealants group, and a shorter OT (MD = −25.49, 95% CI = −50.55 to −0.43, $P = 0.05$) in the gelatin matrix thrombin sealants group than in the suture group. Both of these treatments could not significantly reduce BTR, UL, LOS, EBL, and WIT when compared to the suture group [Supplementary Appendix 5, http://links.lww.com/CM9/A938].

The asymmetric funnel plot with Egger's test indicated that there was a low risk of publication bias for WIT ($P = 0.06$) [Supplementary Appendix 6, http://links.lww.com/CM9/A938]. However, no significant publication bias was found for BTR, UL, and HCs ($P > 0.10$).

This meta-analysis showed no significant changes in BTR, UL, HCs, LOS, EBL, WIT, and OT between the additional HA plus suture and suture groups during minimally invasive PN. However, the results varied across different subgroups of surgical procedures and HA types. The effect of additional HA appeared to be better in LPN than in RAPN.

Additional HA was significantly associated with less UL and HCs after treatment with LPN. On the contrary, no significant differences were found between the two groups after RAPN treatment. The use of additional HA had more obvious advantages in reducing complications in LPN than in RAPN. Based on these results, the most likely explanation may be that RAPN has better post-operative outcomes than LPN due to its continuous development of surgical techniques, improvement of dexterity and visuali-

zation, and more manageable learning curve of suture renography. Renal parenchyma was sutured more accurately by robotic assistance, and sliding-clip technique was often used to avoid tying knots in RAPN, which was sufficient to achieve hemostasis and prevent related complications. Hence, the use of HAs may be obviated during RAPN procedures.

For subgroup analysis based on different HA types, the results showed that HA types appeared to have little effect on post-operative outcomes during PN. Antonelli *et al*[6] reported that there were no significant differences in perioperative outcomes between the TachoSil® and FloSeal® groups during PN procedures.[6] The divergence in these results may be attributed to the impact of different surgical procedures of PN.

"There were significant heterogeneity observed on EBL, WIT, and OT between the additional HA plus suture and suture groups." Pooling of continuous outcomes was easily affected by many factors. For example, EBL could be measured by different methods with varying measurement accuracy, such as weighing method, area method, and volume method. The definitions of WIT and OT might be different in each included study. These factors might be the reasons for the observed high heterogeneity, leading to wide CIs of the pooled effect estimates and no statistically significant differences. Hence, the relevant details of clinical outcomes should be reported in the primary studies for achieving a more effective secondary data analysis.

The average annual HA expenditures of RAPN and LPN were $1452.49 and $626.98, respectively.[7] The use of additional HA could significantly increase national expenses and financial burden on patients who underwent PN, especially RAPN. Considering the lack of better postoperative outcomes and extra costs of HAs, their implementation in RAPN seems highly questionable. Eliminating the use of unnecessary HA may improve the cost-effectiveness of RAPN.

To our knowledge, this is currently the only systematic review and meta-analysis to assess the role of additional HA on the improvement of hemostatic effect and the prevention of surgical complications during minimally invasive PN. However, this study has several limitations that should be acknowledged. First, all included studies were retrospective cohort studies, but the baseline characteristics (eg, tumor size) were similar between the two groups. Thus, selection bias could not be avoided. Second, except for different surgical procedures of PN and HA types, the high heterogeneity among different studies might be attributed to the uneven operative experience of surgeons in different hospitals, dosage of HA, characteristics of patients (eg, tumor location and depth, comorbidity, use of anticoagulant, etc), application of Surgicel® (Ethicon, Cincinnati, OH, USA) bolster, and other details of surgical techniques (eg, type of suture, tumor resection technique, etc). However, these factors were neglected in some of the included studies, so it may be difficult to evaluate their impact on the results. The reporting quality of trials about this topic needs to be improved in the future.

In conclusion, additional HA combined with suture could significantly reduce the occurrence of UL and HCs without increasing WIT and OT in LPN, while no significant differences were observed in RAPN. Therefore, HA may be considered as a supplement to suture in LPN, and its routine use in RAPN is worth reconsideration due to the unimproved effectiveness and increased cost burdens. Nevertheless, our findings need to be verified through highquality, prospective, RCTs in the near future.

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Conflicts of interest

None.

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