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Original Article

The evaluation of a novel technique for in situ cold perfusion in laparoscopic partial nephrectomy

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Abstract: Background: We present our technique, results and experience with in situ continuous cold perfusion of the kidney during retroperitoneal laparoscopic partial nephrectomy (RLPN). Materials and Methods: From October 2012 to March 2015, RLPN was performed in 53 patients (the novel technique group). Of these, 5 patients had a solitary kidney, renal failure in the opposite kidney, or higher preoperative serum creatinine (Cr) levels. Cold ischemia was achieved by continuous perfusion of Ringer's lactate solution at 4°C through the renal artery, which was clamped proximally and pierced directly with a needle. Cold perfusion was initiated via the needle at a rate of 40 ml/min and 2 minutes later, decreased to 15 ml/min. The perfusate was infused into the systemic circulation via the renal veins. Thirty minutes later, 10 mg of furosemide was administered intravenously. The tumor was resected in a bloodless field. After repair of the renal defect, the perfusion was terminated, the needle was withdrawn, the bulldog clamp was removed, and arterial blood flow was reestablished. The patient's vital signs were observed throughout each surgery. The ischemia time and postoperative complications were recorded. Renal function was assessed with Cr values after each surgery, and an ultrasound was performed on the patients to scan the kidneys 6 months postoperatively. Patients (n = 30) who underwent the same surgery without in situ cold perfusion in the same center between June 2010 and June 2012 were reviewed for inclusion in the control group. Data on ischemia time and postoperative Cr levels in the two groups were collected for comparison. Results: All the procedures were successfully completed laparoscopically using the new technique. During the surgeries, no arrhythmia or hemorrhage was observed. No postoperative acute renal failure, leakage of urine, or specific complications related to the perfusion technique were observed. A total of 41 patients (including 4 of the 5 patients described above) underwent at least 6 months of follow-up, and none required dialysis. After 6 months of follow-up, no renal atrophy ultrasound was detected, and the renal parenchymal echogenicity and vascular resistance index were normal. The mean (range) ischemia time in the novel technique group was 47 (24-79) min, significantly longer than the mean (range) in the control group 18 (8-21) min ($P < 0.05$), and the Cr levels showed no differences at different time points after surgery. Conclusion: With this technique, kidney hypothermia can be achieved quickly during RLPN, and the procedure can effectively preserve renal function with few complications. The approach is safe, less demanding, and especially suitable for patients with a solitary kidney, renal failure in the opposite kidney, or preoperative renal inadequacy.

Keywords: Partial nephrectomy, in situ perfusion, laparoscopy, renal neoplasm, ischemia

Introduction

In both open and laparoscopic partial nephrectomy, blocking renal blood flow is usually required to reduce blood loss, maintain a clear operating field, and relieve the time pressure for an accurate operation. Warm ischemia is detrimental to renal function. The current recommendations indicate that warm renal ischemia should be less than 20 minutes with a threshold of 25 minutes [1, 2]. A warm ischemic time of ≥ 25 minutes can cause irreversible damage distributed diffusely throughout the operated kidney [3, 4]. Commonly, cold renal ischemia rather than warm ischemia is used to preserve renal function. Some studies have shown that 20 to 25°C hypothermia provides complete renal protection from ischemia for at least 90 minutes [5, 6]. For the above reason, how to quickly achieve optimal hypothermia of the operated kidney is a critical question in laparoscopic partial nephrectomy. We have developed a new technique for the in situ cold perfusion of kidneys during laparoscopic partial nephrectomy. With this new method, kidney hypothermia can be achieved quickly during

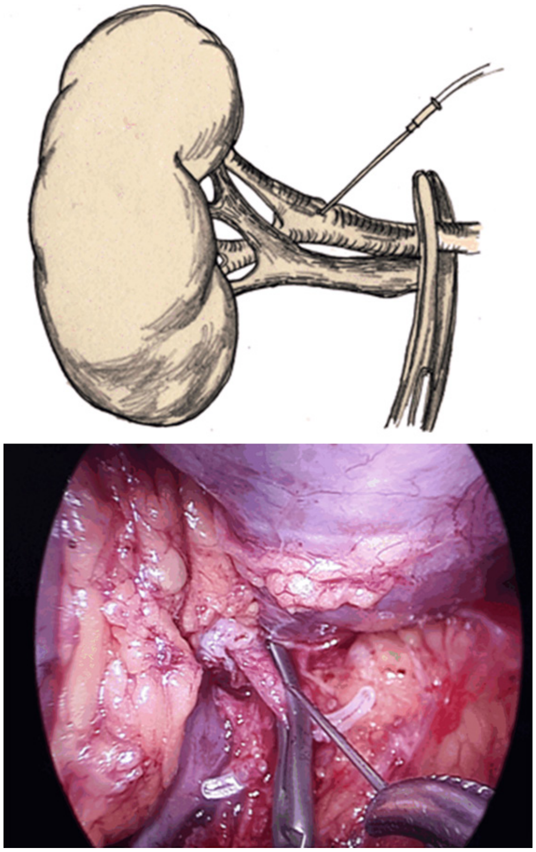

Figure 1. In situ perfusion of the kidney: Cold perfusate is connected to a traditional intravenous tube terminating in a size 5 infusion needle directly piercing the renal artery.

surgery. Furthermore, it is simple, safe and effective.

Patient information

From October 2012 to March 2015, we utilized in situ kidney persistent cold perfusion when performing retroperitoneal laparoscopic partial nephrectomy on patients with renal tumors. Patients were selected according to the following criteria: 1) tumors located on the upper or lower pole of the kidney and diameters ≤ 4 cm or tumors located on the surface of the kidney and diameters ≤ 3 cm based on CT scan; and 2) CTA scans showed that one main renal artery supplies most renal parenchyma. The patients we selected, including 32 males and 21 females, ranged in age from 31 to 67 years old, with a mean age of 45.3 ± 17.5 years old. Thirty cases involved the left kidney, 23 involved the right kidney, and 2 involved a solitary kidney or renal failure in the opposite kidney. Preoperative serum creatinine (Cr) higher than 105 μmol/L was found in 3 cases. Tumor invasion into the collection system was found during surgery in 6 cases. The 53 patients were compared to a historical control group of 30 patients at the same center between June 2010 and June 2012, including 18 males and 12 females ranging in age from 30 to 66 years old, with a mean age of 45.2 ± 17.8 years old. Seventeen cases involved the left kidney, while 13 involved the right kidney. These patients were operated on by the same surgical team.

Surgical approach

Preoperative preparation was performed according to standard practice. General anesthesia was induced in all patients via the tracheal cannula before they were placed in a lateral position and sanitized. Three surgical gaps were established: 1) the intersection of the posterior axillary line and the inferior border of the twelfth rib, 2) the midaxillary line 3.0 cm above the iliac spine, and 3) the anterior axillary line 5.0 cm above the iliac spine. Trocars were placed into the surgical gaps. All laparoscopic procedures were performed by the retroperitoneal approach. Conventional separation of perinephric tissue was performed to expose the kidney and the tumor, as well as to isolate the renal artery. Cold perfusate was connected to a standard intravenous tube terminating in a size 5 infusion needle (**Figure 1**). The needle and the end portion of the perfusion tubing were placed into the surgical field through the right gap (outside of the trocar). Perfusion flow was facilitated by external compression of the irrigation bag with a gas-regulated pressure system, by which the perfusion rate was adjusted, and all air was flushed from the line. As soon as the artery was occluded proximally with a laparoscopic bulldog clamp, it was pierced directly by the fine needle at the distal end at a 45˚ angle, with a depth of approximately 0.8 cm and was perfused with 4°C Ringer's lactate solution via the needle. Perfusion was regulated at a speed of 40 ml/min and was changed 2 minutes later to 15 ml/min. Perfusate was infused into the systemic circulation via the renal veins. Two minutes after the kidney turned pale, the tumor was resected, including normal tissue within a margin of 0.5 cm from the tumor's visible border, with biopsies taken from the tumor bed. After suture-ligating visible vessels, which were easily identifiable by the escaping perfusion fluid, coagulation or an ultrasonic knife was used to stop any minor bleeding. The collection system was stitched with 5-0 absorbable suture. The renal raw surface was compressed with hemostatic material and stitched with 2-0 absorbable suture. Cold perfusion continued throughout the procedure. After repair of the renal defect, perfusion was terminated, the needle was withdrawn, the puncture site was compressed with hemostatic material, and the bulldog clamp was removed. Furthermore, arterial blood flow was reestablished. Patients were intravenously injected with 10 mg of furosemide intraoperatively 30 minutes after perfusion was initiated. The duration of renal artery blockage was recorded, and the kidney wound was checked to determine whether it was secure and whether any active bleeding was present. The stitched renal raw surface was sprayed with biological proteogel. The arterial puncture site was inspected to confirm bleeding and to verify that hemostasis by compression with hemostatic materials was not needed. The tumor was removed, and a drainage tube was placed. Patient vital signs were strictly monitored throughout the surgery. The surgery was completed once the three surgical gaps were stitched. This study was approved by the Ethical Committee of Xinqiao Hospital of Third Military Medical University, and consent was obtained from patients.

Postoperative disposition

The vital signs of all patients were monitored, and complications, such as hemorrhage and leakage of urine, were recorded. Cr levels were measured on a regular basis. If the Cr level was higher than normal (> 105 μmol/L), Cr levels were measured once a day for one week after the surgery, once every other day for two weeks after the surgery, and then once a week. Six months after the surgery, the patients were scanned by a color Doppler ultrasound to observe the presence of renal atrophy, renal parenchymal echogenicity and the vascular resistance index.

Ex vivo studies

In a pilot study, one pig was placed under general anesthesia and prepared for RLPN in a lateral position. The surgery was performed on the left kidney. In the porcine model, renal temperature was continuously monitored with a thermocouple probe located in the parenchyma. A perfusion pump was used to achieve the required perfusion rate. A parenchymal temperature of 22°C was attained during perfusion with iced Ringer's lactate at 4°C at a rate of 40 ml/min for 2 minutes, after which the perfusion was decreased to a rate of 15 ml/min, and a steady state of 22°C so hypothermia could be maintained.

Statistical analysis

Quantitative data are presented as the mean ± standard deviation (SD). Paired and unpaired Student's t tests were performed to compare the data within and between the groups, respectively. All statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

Results

All surgeries were successful. Before each surgery was completed, a check showed no hemorrhaging at the locations where the renal arterial puncture sites were compressed with hemostatic materials. The intraoperative mean hemorrhage volume was approximately 150 ml (ranging from 50 to 300 ml). The mean operative time was 103 minutes (ranging from 88 to 178 minutes). The mean time between blocking the renal artery and the start of in situ kidney cold perfusion was 6 seconds (ranging from 4 to 12 seconds). As perfusion began, the kidney soon turned pale. The mean diameter of the resected tumors was 3.5 cm (ranging from 2.7 to 4.2 cm). Based on postoperative pathological examinations, the results suggested that 47 cases were renal carcinoma and that six cases were renal angiomyolipoma. No tumor cells were detected at the margins of resection. During the surgeries, all patients remained in a stable condition. No extreme fluctuations in heart rate or blood pressure or the occurrence of arrhythmias were observed. There was no hemorrhea, conversion to open surgery, or any other abnormal surgical circumstances. Intraoperative blood transfusions were applied to only two patients. After the surgeries, no secondary hemorrhages and no kidney, perinephric or systemic infections occurred. Furthermore, no leakage of urine, kidney failure or any other acute renal complications was observed.

Table 1. Details of 5 patients with a solitary kidney, renal failure in the opposite kidney, or preoperative renal inadequacy

Case	Age	Postoperative characteristics	Postoperative Cr level (μmol/L)	Cr level at different postoperative time points (μmol/L)						
				d 1	d 3	w 1	w 2	m 1	m 3	m 6
1	37	The contralateral kidney excised due to TB	77	241	212	184	166	158	151	147
2	44	The contralateral kidney with nephrarctia	82	287	234	211	194	177	172	169
3	46	Urine protein ++	128	217	189	180	175	171		
4	65	Urine protein +	154	334	257	232	227	220	232	196
5	54	Urine protein -	119	192	187	178	174	165	152	141

Cr normal value range: 45~105 (μmol/L).

Table 2. Cr levels in the two groups at different time points after surgery

Timepoints after surgery	Novel technique group (μmol/L) $\overline{x} \pm s$	Control group (μmol/L) $\overline{x} \pm s$	*P*-value
d 1	110 ± 13	102 ± 15	0.450
d 3	108 ± 12	110 ± 14	0.329
w 1	98 ± 14	105 ± 11	0.279
w 3	95 ± 13	105 ± 11	0.364
m 1	96 ± 11	95 ± 10	0.378
m 3	85 ± 10	82 ± 11	0.666
m 6	80 ± 12	78 ± 14	0.256

The mean (range) renal ischemia time was 47 (24-79) min, significantly longer than the mean (range) in the control group, which was 18 (8-21) min ($P < 0.05$). The Cr levels showed no differences at different time points after the surgeries, as shown in **Table 2**.

In addition to the 5 patients described above, postoperative Cr levels higher than 105 μmol/L were found in 3 patients, and all returned to normal levels two weeks after the surgeries. A total of 41 cases (including 4 of the 5 patients mentioned above) underwent at least 6 months of follow-up, and none required dialysis. After 6 months of follow-up, ultrasound detected no renal atrophy, and the renal parenchymal echogenicity and vascular resistance index were normal (RI = 0.62~0.74). No patient experienced tumor recurrence or metastasis. The details of the 5 patients with a solitary kidney, renal failure in the opposite kidney, or preoperative renal inadequacy are shown in **Table 1**.

Discussion

Due to the low recurrence rates and excellent survival rates of partial nephrectomy (nephron-sparing surgery) in patients with small renal tumors, this approach is now an accepted alternative to radical nephrectomy [7]. Partial nephrectomy is established as the gold standard operation for renal tumors < 4 cm in size [8]. Furthermore, in cases (imperative indications) with a solitary kidney, synchronous bilateral tumors, renal failure in the opposite kidney, or preoperative renal inadequacy, surgery is the only option for preventing hemodialysis or the need for transplantation [9].

Nephron-sparing surgery (NSS) is usually performed with the kidney under ischemia, which is a risk factor for chronic renal dysfunction after surgery [10, 11]. Ischemia/reperfusion injury (IRI) to the renal parenchyma is one of the major concerns after NSS. Hypothermia is commonly used to protect the kidneys from IRI and has been successfully applied in open NSS [9]. The laparoscopic approach to nephrectomy has gained increasingly wide acceptance in the past few years and is progressively becoming a standard of care for renal cell carcinoma. However, RLPN has been hindered by the lack of a proper method for cooling the kidney for imperative indications and complex procedures in which vascular clamping time is expected to exceed 25 minutes. Thus, a reliable, simple, and quick technique to achieve renal hypothermia during RLPN is urgently needed.

Many significant attempts have been made to achieve renal hypothermia. Initially, some suggested the external use of slush ice or ice-cold saline to cool down the kidney [12, 13]. The disadvantage of this approach is that the temperature in the center of the kidney is still not sufficiently low, and the risk of IRI still exists. Additionally, renal arterial thrombosis may form. Some have suggested intracorporeal renal cooling, which is achieved by cold saline perfusion of the renal pelvis through a single-J ureteral catheter. However, the disadvantage of this approach is that it has low cooling efficiency [14]. Since then, others have tried to use a balloon catheter to block the renal artery by preoperative interventional catheterization from the femoral artery to the renal artery and then allow perfusate to flow through the tube into the kidney to achieve in situ kidney cold perfusion [15-18]. This method does solve the problem of reducing the temperature at the center of the kidney and reduces injury caused by renal ischemia-reperfusion and thrombosis. However, blocking the renal artery by a balloon catheter may cause damage to the arterial wall, such as arterial rupture, aneurysm formation and other serious complications. Additionally, preoperative intervention with femoral arterial catheterization is an invasive procedure. This type of procedure increases not only the recovery time and economic burden to the patient but also the postoperative risks for hemorrhage and infection. Steffens and associates have described a cold ischemia technique [9] in which the hilar vessels are clamped and then perfusion via an arteriotomy and drainage of the perfusate via a venotomy were performed. After 500 ml of cold perfusion, the cannula is removed from the renal artery, and the arteriotomy and venotomy are closed by suture ligation. However, this approach is also complicated, and arteriotomy and venotomy may present some complications, such as intraoperative and postoperative hemorrhage, renal artery stenosis, thrombosis, and other issues. Another cold ischemia technique was reported by Ciara and associates [19]. In their surgeries, before cannulation, the artery was encircled with a Silastic® vessel loop. The renal artery was then cannulated by piercing the Silastic vessel loop. Although this procedure is more simple than preoperative interventional catheterization from the femoral artery to the renal artery, we found that it was still complicated and was difficult to promote.

Instead, we pierced the renal artery directly with a fine needle, which was connected to a traditional transfusion device. This method avoids the redundant procedures of preoperative intervention via femoral artery catheterization or encircling the renal artery with a Silastic vessel loop. Our procedure significantly reduces the pain and economic burden to the patient, and none of the risks associated with intervention are involved. Transfusion needles are very common in the clinic and can be accessed any time during surgery without special preparation. Renal arterial perfusion causes very limited damage to the arterial wall, consequently leading to much lower rates of arterial rupture, aneurysm formation and other serious complications compared to placement of a balloon catheter within the blood vessel. We found that piercing the renal artery with a fine needle intraoperatively to perform in situ kidney perfusion with 4°C Ringer's lactate solution is easy and quick and causes less damage to the vascular wall. As long as proper attention is paid, the needle tip will not come out of the arterial lumen during the surgery.

To quickly and effectively reduce the core temperature of the kidney, cold perfusion was initiated at a rate of 40 ml/min. The cold irrigation solution was infused into the inferior vena cava via the renal veins and was then returned to the heart; therefore, it had the potential to cause arrhythmia and even cardiac arrest. However, these complications were not common because the venous return was approximately 5000 ml per minute. Because the blood temperature is 38°C and the perfusate into the inferior vena cava is 4°C (much higher than 4°C), the temperature of the blood that enters into heart will be at least 37.7°C (Ringer's lactate solution has a similar specific heat capacity to blood). This temperature is much higher than 35°C and may cause arrhythmia and even cardiac arrest. However, similar approaches have been reported to be safe [18, 19]. In this study of 53 patients, during the surgeries, all patients had normal heart rates and blood pressure levels, with no arrhythmia. These findings prove that this method of in situ kidney cold perfusion causes no damage to the cardiovascular system.

Under physiological conditions, the renal blood flow is 600-800 ml/min. In this study, the fastest infusion speed was 40 ml/min. Thus, the irrigation compression was much lower than the normal pressure in the vessels, which was safe for the operated kidney.

As approximately 500 ml of Ringer's solution had been perfused into the body 30 minutes after perfusion, 10 mg of furosemide was administered intravenously to reduce the load on the heart. With this procedure, no time pressure was imposed on the surgeries for complex tumors when the ischemia time needed to be longer than expected.

No intraoperative or postoperative hemorrhage was observed at the arterial puncture site. Moreover, no specific complications related to the perfusion technique were found after the surgeries. Human tissue basal metabolism can be decreased by approximately 6~7% as the tissue temperature drops 1°C. When the temperature drops to an optimal level of 25°C, renal function can be effectively protected [5, 6]. Although the intraparenchymal temperature of the operated kidney was not monitored intraoperatively, no acute or chronic kidney failure was observed postoperatively, and ultrasound examinations after 6 months of follow-up showed no kidney atrophy and a normal renal arterial resistance index (RI), which indicated no significant IRI morphologically. Furthermore, no renal failure occurred in the five patients with imperative indications after surgery. Although the postoperative Cr levels increased in all of them, none required dialysis, and the Cr values were shown to continually decrease with time. Thus, the hypothermia achieved by our technique can effectively protect the renal function of the operated kidney.

Conclusions

This technique is an effective method for protecting renal function during RLPN. With this approach, hypothermia of the operated kidney can be quickly achieved, and no time pressure is imposed on the accuracy of operations when the ischemia time needs to be longer than expected. This procedure is safe, simple and less demanding than previous procedures, and it is especially suitable for patients with a solitary kidney, renal failure in the opposite kidney or preoperative renal inadequacy.

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Disclosure of conflict of interest

None.

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