Published in final edited form as:

BJU Int. 2012 September ; 110(6B): E274–E280. doi:10.1111/j.1464-410X.2012.10967.x.

Temporary targeted renal blood flow interruption using a reverse thermosensitive polymer to facilitate bloodless partial nephrectomy: a swine survival study

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Abstract

- To examine whether randomly selected regions of the kidney could undergo temporary flow interruption with a reverse thermosensitive polymer (RTP), Lumagel™ (Pluromed, Inc., Woburn, MA, USA), followed by partial nephrectomy (PN), without adding risks beyond those encountered in the same procedure with the use of hilar clamping.
- A two-armed (RTP vs hilar clamp), 6-week swine survival study was performed.
- Four swine underwent PN using hilar clamps, while six underwent PN with flow interruption using the RTP.
- The RTP, administered angiographically, was used for intraluminal occlusion of segmental or subsegmental arteries and was compared with main renal artery clamping with hilar clamps. The resection site was randomized for each swine.
- Laboratory studies were performed preoperatively, and at weeks 1, 3 and 6.
- Before killing the swine, repeat angiography was performed with emphasis on the site of previous flow interruption.
- Gross and microscopic examination of kidney, liver, lung, heart, skeletal muscle was later performed, and the vessel that had supported the previous plug was examined.
- All animals survived. No abnormal chemistry or haematology results were encountered over the 6 weeks. There were no surgical complications in either group.
- Using angiography we found 100% patency of vessels that had been occluded with the polymer 6 weeks previously for PN. The only gross or microscopic abnormalities were related to the renal resection and scar formation, and were similar in the two groups.
- Targeted flow interruption with the RTP added no additional risk to PN while allowing bloodless resection and uninterrupted flow to untargeted renal tissue.

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FINANCIAL DISCLOSURE

James A. Benn and Peter N. Madras disclose a financial interest in Pluromed, Inc. Rosanna Villani discloses a financial interest in DaVinci Biomedical Research Products, Inc.

Keywords

partial nephrectomy; minimally invasive; warm ischaemia

INTRODUCTION

Partial nephrectomy (PN) is a standard treatment for patients with bilateral RCC or cancer in a solitary kidney, and is gaining rapid acceptance for most solitary cancers < 4 cm [1,2]. Currently, it is recognized that minimally invasive (MI) PN provides a shorter length of hospital stay, less postoperative analgesic requirement, and earlier convalescence compared with open surgery [3,4]. Both open and MI techniques are facilitated by temporary blood flow interruption, typically accomplished by hilar clamping, but the duration of flow interruption may be longer when using a MI technique [5,6]. Longer warm ischaemia time has been associated with worse short- and long-term renal function as well as more overall complications after surgery [7–10].

Work from our laboratory using Lumagel™ (Pluromed Inc., Woburn, MA, USA, a reverse thermosensitive polymer (RTP), in an acute setting, has led to the development of reproducible techniques to interrupt blood flow to targeted regions of the kidney destined to undergo resection, while maintaining continuous flow to the uninvolved ipsilateral renal tissue [11]. In the present study, we compared these techniques with hilar clamping for PN in 10 surviving swine. The purpose of this 6-week survival study was to determine whether PN performed with the RTP was as safe as hilar clamping, with its advantage of retaining blood flow to uninvolved portions of the kidney.

MATERIALS AND METHODS

The experiments were approved by the IACUC of DaVinci Biomedical Research Products, Inc (South Lancaster, MA, USA). This was a descriptive, randomized, pathologist-blinded study, in which the selection of resection site was made after induction of anaesthesia but before angiographic data were obtained. Randomization was achieved by two coin tosses: the first determined laterality, the second, polarity. All animals underwent standard anaesthesia and monitoring.

Ten Yorkshire swine, weighing 39.8 ± 1.28 kg, underwent PN via a flank incision: four control swine underwent hilar dissection and renal artery cross-clamping (control group) and six swine underwent renal artery catheterization and segmental or subsegmental arterial branch interruption using the RTP (RTP group).

At 6 weeks, immediately before being killed, all swine underwent repeat angiography with emphasis on the exact site of previous plug deposition in the RTP group, and the main renal artery in the control group. After the swine were killed, organs were harvested (kidney, liver, spleen, lung, heart, intestine and skeletal muscle), placed in coded containers and delivered to the pathologist who remained blinded until the final report was issued. Specimens were also frozen in liquid nitrogen and retained for future examination if required by findings on pathology.

All cases using the RTP were performed with the assistance of an interventional radiologist for renal vasculature access and interpretation of radiographic images. Our operative technique consisted of placing a central venous catheter in the internal jugular vein for venous access. In the six animals in which the RTP was used, a vascular sheath was introduced into the femoral artery using the Seldinger technique, and advanced into the iliac

artery. The swine was then placed in a flank position. The kidney was dissected in a retroperitoneal fashion with hilar dissection completed only in those swine undergoing renal artery clamping. Under direct fluoroscopic guidance, the renal artery was catheterized with a 7-F guiding catheter (Veripath; Abbott Laboratories, Abbott Park, IL, USA). A hand-injected aortogram and renal angiogram were obtained to determine which segmental or subsegmental renal branches required occlusion. A heparinized saline solution was continually infused through the side arm of the introducer and a Tuohy--Borst-type adapter (rotating haemostatic valve, 0.096 inch; Abbott Vascular, Santa Clara, CA, USA) attached to the guiding catheter. Selective angiography of the renal artery was performed using a 5-F angiography catheter (C2 Cobra; Cook, Bloomington, IN, USA) which was co-axially introduced through the guiding catheter [12]. A specially designed hand-held injector was used to allow precise injection of the RTP using real-time fluoroscopic visualization of the forming plug. Unintended 'spillover' occlusion of neighbouring vessels was carefully avoided, and readily reversed in the one case in which it occurred. After satisfactory injection and placement of the polymer plug, the catheter was removed and a repeat angiogram performed to verify the extent and integrity of the occlusion. This marked the start of haemostasis and was manifested on gross inspection as a demarcation line between the normal pink colour of the perfused portion of the kidney and a pale or white colour visible in the treated section. PN was performed by simply cutting through the kidney without regard to underlying structure, resecting $\approx 15\%$ of the renal parenchyma. Major vessels and openings in the collecting system were closed with absorbable sutures, and the kidney was closed over a bolster of gel foam and thrombin.

After PN, the residual plug was dissolved by infusion of iced saline through the angiographic catheter. Dissolution of the RTP plug and reperfusion of blood flow were observed via angiogram. After radiological confirmation of reperfusion, visual observation of the kidney was used to affirm haemostasis. The wound was closed in layers using interrupted polypropylene sutures. The swine were awoken from anaesthesia and maintained and housed for 6 weeks after surgery. Blood samples (complete blood count, electrolytes, renal and hepatic function tests) were drawn preoperatively, and at weeks 1, 3, and 6.

After 6-weeks, the animal was anaesthetized and arteriography was performed duplicating the baseline technique. The final arteriogram was compared with the baseline study to ensure that the exact site of plug deposition was readily identifiable. Blood samples were sent and the swine were killed. A complete necropsy was then performed via a midline incision. The treated kidney was submitted uncut and specimens of the untreated kidney, liver, lungs, heart, spleen and a portion of pectoral major muscle were submitted. Additional samples from harvested organs were flash frozen and stored at 80°C . All samples were stored in coded containers to blind the pathologist. For the resected kidney, serial sections at 0.5-cm intervals were prepared from the resection margin to the hilum. Each slice was examined under hand lens for scarring, luminal obliteration, infarction, haemorrhage or discoloration. Areas of interest in the kidney were stained with H&E, trichrome, Jones, and PAS. Elastic tissue stains were also used. All other tissues were stained with standard H&E. The extent of the pathology changes were scored as shown in Table 2. After the final pathology report was complete, the pathologist was unblinded and the pathology score was correlated to the control vs the RTP group. All surgical procedures as well as housing, care and follow-up tests were conducted at DaVinci Biomedical Research Products, Inc.

RESULTS

All swine survived for the 6-week follow-up period. Table 1 shows the surgical outcomes of the 10 swine experiments. The mean weight gain was 17.1 kg, with the RTP group gaining 18.4 kg, and the clamp group gaining 15.2 kg. In the RTP group four of the six swine had

been randomized to a right lower pole resection, the others to a left upper and left lower pole resection. One of the right upper pole resections required occlusion of three feeding subsegmental renal vessels (Fig. 1). The four swine in the control group were not randomized as to resection site since complex vascularity would not be a factor in this group. Instead, these swine underwent left upper and lower, and right upper and lower pole amputations. The mean ischaemia time in the control group was 7.75 min.

The mean volume of RTP required for occlusion was 0.9 cc. This excludes the volume required to prime the catheter, which was also 0.9 cc. It is important to re-emphasize that the actual volume of RTP injected was determined by visualizing the plug forming in real time under fluoroscopy, but the recorded volume was taken from reading the syringe markers on completion of the injection and may have been a slight overestimate, as described in the discussion below. In swine #9, an instructive technical problem developed which made the estimate of volume impossible. Owing to a break in the Leur-lock hub of the arterial catheter, it dislocated from the syringe. On replacing and fixing the catheter to the injector, an injection of RTP was made in haste, and a large volume was administered inadvertently, which, on angiography, was immediately shown to have completely blocked the main renal artery and all its proximal branches. Using iced saline infusion, in < 3 min, the unintended RTP was dissolved while the targeted vessel remained occluded and the intended PN was completed uneventfully. This swine had no measureable adverse systemic or renal outcomes. The mean duration of the procedure was 43.5 min in the control group and 64.6 min in the RTP group. The mean additional time required for the application of RTP was 13.6 min before the start of renal resection and 5 min for plug dissolution.

Laboratory analysis consisted of a complete blood count, electrolytes, and renal and liver function tests; no significant differences were noted between the two groups. Surprisingly, the serum creatinine concentration trended slightly higher in the control group but was unchanged in the RTP group. Interestingly, all swine sustained a drop in haematocrit, (control group: mean $19 \pm 8\%$; RTP group: mean $24 \pm 4\%$) which was to be expected with swine maintained indoors for this period of time.

Angiography 6 weeks after injection allowed examination of the exact site of the RTP deposit, where the plug had been occlusive for 20--30 min (Fig. 2). In five pigs no changes were seen, while one angiogram showed arterial spasm (Fig. 3). The only consistent difference between baseline and 6-week angiograms was the absence of terminal small branches which had been resected as part of the earlier PN.

At necropsy, no abnormal anatomic or microscopic changes were seen. Consistent with the findings of pre-terminal angiography, the segmental branch of the renal artery, which 6 weeks previously had enveloped the RTP plug, showed no endothelial damage, no hyperplasia and no suggestion of resolving thrombus or thrombotic material. One liver from each of the control and the experimental groups showed minimal portal and lobular inflammation; one experimental and two control swine showed peribronchial lymphoid follicles. None of these changes were related to the use of RTP. Heart, spleen, contralateral kidney and skeletal muscle were normal. Most importantly, the renal tissue that was not excised but was nevertheless in the downstream distribution of the blocked vessel showed no features to distinguish it from the normal remaining renal tissue which had never been exposed to the RTP.

DISCUSSION

In earlier acute studies, we described techniques using RTP (Lumagel™) for performing bloodless PN while maintaining circulation to untargeted regions of the kidney [11];

however, long-term outcomes after the use of RTP remained unaddressed. Because the plug remained in contact with the wall of a small artery (1.3--3.0 mm) for ≈ 20 min, the possibility of arterial injury including thrombosis, intimal hyperplasia, elastic lamellar disruption, and necrosis or aneurysm formation remained. In addition, insult to renal tissue downstream of the plug, which would have been exposed to the highest concentration of both RTP and contrast agent, was considered. No gross or microscopic harm from the previous sustained RTP contact was observed in either of these vulnerable tissues.

Earlier flow model studies of Lumagel™ plugs led to the generalization that plug stability lasted for at least 30 min, in a straight vessel requiring a length to diameter ratio (LDR) of 10. This would ensure a comfortable duration of flow interruption for bloodless PN but an LDR equal to 10 may not be possible *in vivo* owing to branching or bifurcation. Fortunately, both of these appear to stabilize a plug, avoiding the need for strict adherence to the LDR of 10. Ultimately, the final length and shape of the plug is determined by the local arterial anatomy and by the experience of the interventionalist.

It has been suggested that small microemboli may form either before the plug becomes apparent or on plug dissolution, but we found no evidence of this on blood tests or pathological examination. Likewise, previous experience in 99 coronary arteries of 50 patients with a very similar compound, (LeGoo™ Pluromed, Inc.) detected no downstream myocardial damage using EKG criteria, measurements of cardiac enzymes and troponins, nor was there evidence of pulmonary embolus clinically [13–15]. Theoretically, if microemboli were to form, the spontaneous dissolution of RTP in whole blood at body temperature would ensure their disappearance in seconds or minutes. Finally, complete necropsy failed to reveal any evidence of pulmonary embolism in any of the swine.

No arterial or arteriolar changes were related to the RTP. There was no thrombosis of the previously occluded vessels, and the thrombi seen in two control and one RTP swine were related to the proximity of these vessels to the operative field, where they were involved in the healing reaction. Two arteries in both the control and the RTP group showed plications or fragmentation of the elastic lamina and three small arteries contained thrombus: two in the control and one in the RTP group. This fragmentation of the elastic tissue was also seen in both groups, and was not related to the use of RTP. In addition to the variables shown in Table 2, changes were examined in the glomerular basement membranes, Bowman's capsule, and the scar itself. Surprisingly, small regions of sclerosed glomeruli were seen in both control and RTP swine, but the finding was not different between the two groups. Hypoperfused glomeruli were noted, as was inflammatory change in the region of the scar. These examinations were all completed while the pathologist remained blinded. After unblinding, no pathology findings clustered preferentially into one group.

The benefits of uninterrupted blood flow during PN are gaining recognition and motivating the search for techniques to accomplish this [16]. Benway et al. [17] describe robotic dissection of the segmental branch of the renal artery to induce polar ischaemia in the swine kidney. Simon *et al.* [18], supported by Viprakasit et al. [19] use a parenchymal clamp specifically designed for laparoscopic application. Shen et al. [20] used a small balloon placed in a renal artery to obtain targeted flow interruption in PN in patients. However, in that study they obtained renal pedicle control and used the balloon-tipped catheter, more to ensure continuous hypothermic perfusion than to interrupt blood flow. Gill et al. [21,22] recently described the use of pharmacologically induced hypotension to avoid ischaemic damage to the kidney. This proliferation of techniques for reducing renal ischaemia attests to the need and anticipated benefit of reliable targeted renal blood flow interruption while sparing flow to the unaffected nephrons. Unlike all other methods for achieving this aim, the use of RTP has the following advantages: it allows targeting of vessels down to 1mm for

super selective blood flow interruption; it can be deployed in multiple vessels if necessary; it is not dependent on the anatomy of the renal vasculature to obtain flow interruption; and there appears to be no toxicity associated with its use. Limitations of the technique would include the need for use of contrast agent, which may have to be limited in patients with renal insufficiency. We used a mean quantity of 300cc of contrast agent for each experiment, but this volume was higher than would be expected for clinical use because of the need to ensure and document stability of the plug as well as the experimental nature of the procedures. Other smaller risks would include the radiation risk secondary to fluoroscopy (mean exposure of 300--1000 mGy) and risk of arterial access which has recently been reported at 0.03% [23]. We did not encounter any complications or adverse events with percutaneous access to the femoral artery, but there is always potential for complications when gaining percutaneous access to a vessel including bleeding, infection, and haematoma formation.

In planning for clinical use of the RTP technique, any candidate (with a suitable estimated GFR) for this treatment would undergo CT angiography and subsequent three-dimensional reconstruction of those images. This would allow precise definition of exactly those segmental branches that would require flow interruption without subjecting the patient to further testing, as the CT scan is a part of the standard evaluation for PN. While early clinical application would be limited to small lesions near the poles of the kidney and perfused by a single vessel, experience in the present study shows that it is not difficult to occlude multiple vessels if necessary, particularly if the exact branches requiring occlusion are known preoperatively.

A potential limitation of the present study is that the work centered on normal kidneys in a swine model and perhaps the vascular configuration of a renal tumour would be more complex with increased risk of bleeding. However, our precise ability to select segmental and subsegmental arteries is unique to our technique for producing targeted haemostasis. Another potential limitation is our measurement of serum creatinine concentration as a marker of renal function. Serum creatinine concentration is influenced by muscle mass and can be affected by variations in diet and catabolic rate. It might have been more beneficial to calculate estimated GFRs, although typical formulas used are not suited for animals. Finally, the present study might be underpowered to detect small differences in the laboratory values between the two groups.

All experiments were performed in the flank position which gave almost instantaneous access to the hilum of the kidney in the pig. Thus, the additional 13 min required for the RTP procedure in these experiments was not offset by the time for hilar dissection, as would be the case in humans. While there is the small risk of possible dislodgement of the femoral access during positioning, we did not encounter this problem. We had no problems concerning space for the surgeon(s), interventionalist, and equipment needed in the operating room. The requirement for fluoroscopy and angiography, while adding to the complexity of the proposed procedure, also obviates the need for hilar dissection.

Since the complication rate of PN performed using conventional techniques in the healthy swine is very low, it was not our purpose in the present study to show greater safety, better outcome or fewer complications with the use of RTP. The goal was to show that, in spite of the need for femoral arterial catheterization and renal angiography, the advantage of continuous blood flow to uninvolved renal tissue and bloodless resection may come at no additional risk over hilar dissection and clamping. The results of the present study support the hypothesis that use of an RTP does not pose increased risks and on that basis, plans are underway for possible clinical studies.

In conclusion, the RTP produced reliable blood flow interruption to regions of the kidney targeted for flow interruption, facilitating bloodless PN while maintaining continuous, uninterrupted perfusion to the uninvolved renal tissue. In this 6-week survival study, there was no systemic toxicity manifested by changes in growth, nutrition, behaviour, renal or hepatic function. No angiographic or pathological evidence of vascular injury at the site of plug deposition was noted after the 6 weeks. The RTP, when used according to the methods in the present study, appears to be as safe as hilar clamping. Preparations are underway for clinical use.

What is known on the subject?

Lumagel™ is a reverse thermosensitive polymer (RTP) that has previously been described in the literature as providing temporary vascular occlusion to allow for bloodless partial nephrectomy (PN) while maintaining blood flow to the untargeted portion of the kidney. At body temperature, Lumagel™ has the consistency of a viscous gel but upon cooling rapidly converts to a liquid state and does not reconstitute thereafter. This property has allowed for it to be used in situations requiring temporary vascular occlusion. Previous experience with similar RTPs in coronary arteries proved successful, with no detectable adverse events.

What does the study add?

We have previously described our technique for temporary vascular occlusion of the main renal artery, as well as segmental and sub-segmental renal branches, to allow for bloodless PN in either an open or minimally invasive approach. These experiments were performed in the acute setting. This study is a two-armed survival trial to assess whether this RTP is as safe as hilar clamping for bloodless PN. Surviving animals showed normal growth after using the RTP, absence of toxicity, no organ dysfunction, and no pathological changes attributable to the RTP. We conclude that Lumagel™ is as safe as conventional PN with hilar clamping, while adding the advantage of uninterrupted perfusion during renal resection.

Acknowledgments

This work was supported by NIH **SBIR Grant**: 1R43DK079481-01.

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Abbreviations

RTP	reverse thermosensitive polymer
PN	partial nephrectomy
MI	minimally invasive
LDR	length to diameter

Fig. 1. Three vessels requiring separate plugs. This case was randomized to a right upper pole resection. Note immediate branching of the segmental branch to the upper pole precluding RTP use in this segment. Individual branches to the upper pole (arrows) required independent plugs.

Fig. 2.

Baseline and 6-week angiography. **A**, A subtraction renal angiogram in a kidney randomized to undergo a right lower pole resection. The arrow highlights a single branch to the lower pole serving as an ideal target for RTP plug formation. **B**, An unsubtracted image of the RTP plug which completely obstructed flow (arrow) to the lower pole, allowing uneventful bloodless lower pole PN. Total plug time was 22 min. **C**, A subtraction image showing no abnormality in the exact arterial segment which had been plugged 6 weeks earlier. This image shows truncation of the terminal vessels (arrow) when compared to panel A, consistent with a 15% lower pole PN. These findings were repeated in five of the six pigs, with Fig. 3 showing the only exception.

Fig. 3.

Baseline and 6-week angiography showing beading in the experimental artery. **A**, Single segmental branch (arrow) to the lower pole of the right kidney (subtracted angiogram). **B**, RTP plug (arrow) placed in the lower segmental branch of the main renal artery. (unsubtracted image of stationary plug). **C**, Segmental branch at 6 weeks (arrow) showing vasospasm in the region previously accommodating the RTP plug. This was the only 6-week angiogram that was not identical to the baseline study, but we note that there were no pathological vascular changes in this swine and that vasospasm was occasionally encountered in baseline studies (Fig. 1). This is considered an incidental, but not adverse finding. In other acute experiments arterial spasm was also encountered and was temporary.

Table 1

Summary of animal experiments

Experiment no.	Start weight, kg	End weight, kg	Weight gain, kg	% gain	Group	Side*	Pole [†]	Delivered RTP volume	Estimated blood loss [‡]	Length of operation, h:min	No. of arteries feeding [§]
1	37.5	51.5	14	37%	RTP	L	U	1.2	1	1:16	3
2	38.7	51.5	12.8	33%	RTP	R	L	0.7	0	1:03	1
3	40.8	53.5	12.7	31%	CTL	L	L	0	0	0:43	NA
4	38.5	54.4	15.9	41%	CTL	R	U	0	0	0:46	NA
5	41.4	49.8	8.4	20%	CTL	R	L	0	0	0:41	NA
6	39.6	58.8	19.2	48%	RTP	L	L	0.9	0	1:04	1
7	40.2	64	23.8	59%	RTP	R	L	0.7	0	1:02	1
8	40.2	63.9	23.7	59%	CTL	L	U	0	1	0:44	NA
9	41.4	63.1	21.7	52%	RTP	R	L	NA	0	1:02	1
10	39.6	58.5	18.9	48%	RTP	R	L	1	0	1:01	2
RTP group mean	39.5	57.9	18.4	47%				0.9		1:04	
Control group mean	40.2	55.4	15.2	38%						0:43	
Group mean	39.8	56.9	17.1	43%						0:56	

L, left; R, right; U, upper; L, lower.

* Selected sequentially for group 1, randomly for group 2.

[†] Selected sequentially for group 1, randomly for group 2.

[‡] 0, no perceptible bleeding; 1, minimal blood loss controlled easily with suture ligation. The remaining scale referred to measurable volumes that did not occur. This blood loss estimate refers only to the loss during renal surgery, not total operative loss, which was also minimal.

[§] Refers to the number of arterial branches requiring occlusion to attain flow interruption to the targeted segment.

Table 2

Pathological findings in scar area

Swine no:	Group	Kidney operated	Total glomeruli in the sample	Sclerosed glomeruli, %*	Fragmentation /Plications of elastic lamina	Non-occlusive or segmental thrombosis
505	Control	Right	338	5.6	0	single vessel
506	Control	Right	192	17.2	0	absent
511	Control	Left	264	4.5	1	absent
512	Control	Left	190	13.7	1	single vessel
507	RTP	Left	200	19	1	absent
508	RTP	Right	214	15	0	absent
510	RTP	Left	201	16	0	absent
513	RTP	Left	99	17.2	1	absent
514	RTP	Right	219	9.1	1	single vessel
515	RTP	Right	285	17.2	0	absent

* Mean % of control group: 10.3 ±6.188; mean of RTP group: 15.6 ± 3.448%; $P=0.11$.