Investigations of a Thermosensitive Gel to Temporarily Occlude Crural Arteries in Femoro-distal Bypass Surgery

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WHAT THIS PAPER ADDS?

Operative and short-term post-operative outcomes show that performing clampless distal anastomosis in peripheral vascular bypass with reverse thermosensitive gel is effective, technically worthwhile and safe.

Objectives: Long occlusions in calcified crural arteries are a major cause of endovascular technical failure in patients with critical limb ischaemia. Therefore, distal bypasses are mainly performed in patients with heavily calcified arteries and with consequently delicate clamping. A new reverse thermosensitive polymer (RTP) is an alternative option to occlude target vessels. The aim of the study is to report our technical experience with RTP and to assess its safety and efficiency to temporarily occlude small calcified arteries during anastomosis time.

Methods: Between July 2010 and December 2011, we used RTP to occlude crural arteries in 20 consecutive patients with 20 venous distal bypasses. We recorded several operative parameters, such as volume of injected RTP, duration of occlusion and anastomotic time. Quality of occlusion was subjectively evaluated. Routine on-table angiography was performed to search for plug emboli. Primary patency, limb salvage and survival rates were reported at 6 months.

Results: In all patients, crural artery occlusion was achieved with the RTP without the use of an adjunct occlusion device. Mean volume of RTP used was 0.3 ml proximally and 0.25 ml distally. Mean duration of occlusion was 14.4 $\pm$ 4.5 min, while completion of the distal anastomosis lasted 13.4 $\pm$ 4.3 min. Quality of occlusion was judged as excellent in eight cases and good in 12 cases. Residual plugs were observed in two patients and removed with an embolectomy catheter, before we amended the technique for dissolution of RTP. At 6 months, primary patency rate was 75% but limb salvage rate was 87.5%. The 30-day mortality rate was 10%.

Conclusions: This study shows that RTP is safe when properly dissolved and effective to occlude small calcified arteries for completion of distal anastomosis.

Article history: Received 8 August 2012, Accepted 4 October 2012, Available online 3 November 2012

Keywords: Critical limb ischaemia, Distal bypass, LeGoo, Reverse thermosensitive polymer, Vascular occlusion

Peripheral arterial disease (PAD) is highly prevalent and usually associated with diabetes, smoking, hypertension or chronic kidney disease (CKD). PAD is often asymptomatic and detected by a decrease of the ankle brachial index (ABI). However, 10—35% of patients with PAD present with intermittent claudication. Only 1—5% of patients have a severe PAD manifested by critical limb ischaemia (CLI).[1] In these patients, revascularisation procedure leads to reduced amputation risk. Different series have shown 5-year limb salvage rates varying between 48% and 63% with 5-year primary patency rates between 41% and 58% after distal bypass for CLI.[2—4]

Nowadays, the endovascular approach for CLI is the first line in many vascular centres. The strategy depends on many factors such as autogenous vein conduit availability, type and length of arterial occlusions and life expectancy. Long occlusion in heavily calcified crural arteries is a major cause of endovascular technical failure and selection for distal bypass. Indeed, due to improvement in endovascular surgery and its increasingly extensive area of application, distal bypass is now exclusively required in very complex cases, which are precisely long occlusions in extremely calcified small arteries, as well as multi-operated patients with endovascular failure. Nevertheless, calcification at the site of anastomosis represents also a risk of technical failure during bypass surgery, mainly due to the presence of calcified plaque that prevents an adequate clamping.[5] Suturing is yet difficult in small calcified crural arteries and the anastomosis completion requires a bloodless field, which is achieved

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1078-5884/$ — see front matter

http://dx.doi.org/10.1016/j.ejvs.2012.10.005

traditionally with clamps, loops or intravascular catheters. But all of these standard devices have drawbacks.[6—11] In fact, they cause endothelial lesions with plaque disruption, leading to potential mid-term development of intimal hyperplasia.[12,13] External occlusion devices may occlude poorly the heavily calcified arteries when they are simultaneously handled with care to spare vessel-wall integrity. Finally, they require extended dissection of the artery, which is time consuming and leads also to bleeding from the periarterial venous network. The occlusion catheters usually achieve an excellent occlusion but have the major disadvantage of obstructing the operative field.

Therefore, the use of a reverse thermosensitive polymer (RTP) (LeGoo™, Pluromed, Woburn, MA, USA), which is viscous at room temperature but turns to gel at 37 °C, could be an alternative to the devices in small distal heavily calcified arteries.[14] Indeed, the intravascular administration of RTP results in an occlusive plug that conforms to the contour of the lumen, allowing the surgeon to work in a bloodless field.

RTP is an aqueous solution comprised of 20% fractionated poloxamer 407 in saline that has the physical property to transition from liquid to gel-form at body temperature. Once in the vessel, it degrades spontaneously by physical 'erosion' that makes this water-soluble polymer reversing back to micelles and then to unimers, with no possibility for it to turn back into a gel at physiological temperatures. Poloxamer 407 is a nontoxic, nonabsorbed and non-metabolised polymer that is excreted through the kidney.[14]

RTP is supplied in pre-filled syringes as a sterile single-use product and is available in multiple volumes to accommodate the vessel size and desired plug length (Fig. 1). The polymer is delivered proximally and distally to the anastomosis and in potential collateral branches. The plug either dissolves spontaneously after several minutes or can be dissolved instantly by cooling, via application of cold saline into the vessel. As already mentioned, RTP cannot create a new plug once dissolved. If the plug dissolves spontaneously before completion of the anastomosis, additional injections can extend the occlusion time.

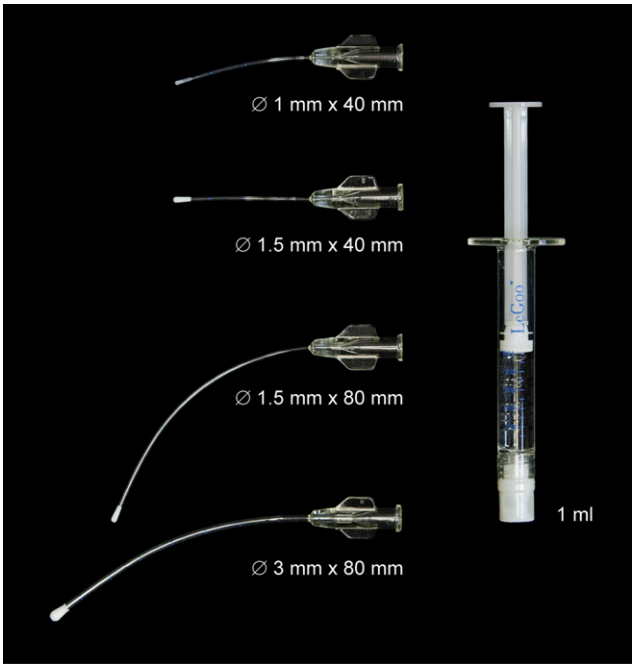

Figure 1. RTP gel LeGoo. Syringe and cannulas with diverse outer diameters.

Previous studies have demonstrated in cardiovascular surgery in animals that RTP preserves endothelium and vascular reactivity, without embolisation into a distal vascular bed.[15,16]

The purpose of this study was to evaluate the efficacy and safety of RTP for the temporary occlusion of crural vessels during distal bypass surgery in patients with CLI.

METHODS

Between December 2010 and July 2011, we included 20 consecutive patients with CLI Rutherford 4—6. The only significant exclusion criteria were chronic kidney disease stage 4 and incapacity of discernment. A pre-operative CT angiogram and vein duplex mapping were obtained for all patients. The endovascular first-line therapy is the strategy of choice in our department. However, long occlusions of crural arteries associated with occlusion of the tibial trunk and below-the-knee popliteal artery are usually treated by femoro-distal bypasses.

Three vascular surgeons performed the interventions; all were already familiar with RTP vessel-occlusion technique. We used RTP only in crural arteries before performing the distal anastomosis.

We recorded any other device used to occlude the artery due to failure of RTP. After completion of the distal anastomosis, we performed routine on-table angiography to assess possible embolisation of RTP in the distal artery, which was compared to pre-operative images.

This study was approved by the Ethical Committee of the University Hospital of Lausanne. All informed consents were obtained before inclusion of the patients.

Surgical procedures

All revascularisation procedures were performed under general or loco-regional anaesthesia. Heparin (50 UI kg^{-1} of body weight) was administered before clamping arteries. The occluded target crural artery was minimally dissected to perform the distal anastomosis. The diameter of the target artery was estimated and the appropriate syringe and cannula to inject RTP were selected according to the manufacturer recommendations. After the arteriotomy, we inserted the cannula distally and injected a volume of RTP in order to occlude the vessel totally (Fig. 2). During the injection, the cannula was withdrawn slowly from the lumen. This was also done proximal to the anastomosis. Bleeding from side branches was controlled by direct injection of RTP into the orifice of the offending branch. After the total occlusion of the lumen with RTP, the vein was sutured to the artery with a continuous 7—0 polypropylene. If the RTP plug dissolved before completion of

Figure 2. Vascular occlusion with plug formation after RTP gel injection.

the anastomosis with recurrent bleeding, additional RTP was injected to restore the plug. At the end of the suture, the RTP plug was dissolved with an intraluminal injection of sterile cold saline solution. The backflow bleeding was assessed before snugging the continuous suture to be sure that the plug was dissolved. On-table arteriography was performed using a micropuncture set (Cook Medical, Bloomington, IN, USA) with an injection of 5–10 ml of iodinated contrast (Visipaque 270, GE Healthcare, Pittsburg, PA, USA) through the vein conduit. The proximal anastomosis was then achieved with the use of a traditional occlusion device.

We recorded the volume of RTP injected proximally and distally in the target vessel, number of required injections as well as duration of occlusion. Furthermore, duration of the surgery and anastomotic time were also noticed. Quality of lumen occlusion by RTP was classified such as: excellent = no bleeding; good = minimal bleeding, anastomosis performed without substantial use of accessory occlusion device; fair = moderate bleeding, anastomosis performed with substantial use of another occlusion device; poor = profuse bleeding, anastomosis performed with continuous use of another occlusion device.

Post-operative follow-up

All patients were followed up with a duplex scan at 1 week, 1 month, 3 months and 6 months post-operatively to evaluate the patency of the bypass. Duration of hospitalisation for each patient was recorded.

Statistics

Descriptive data are expressed as mean, standard deviation and range values. Percentages are given when appropriate. Deaths were censored with no follow-up.

RESULTS

We performed 20 distal bypasses in 20 consecutive patients. There were five female and 15 male patients, with an average age of 81 years (range 45–94 years). Five patients (25%) were diabetic and three (15%) had CKD stage 5. Patient characteristics are listed in Table 1.

Proximal anastomoses were performed at the femoral or at the above-the-knee popliteal arteries and distal anastomoses were all performed at the crural arteries (see Table 2). Venous conduits were used for all bypasses. RTP was used in all patients to occlude the crural artery without the need of any other occlusion device. Mean volume of RTP used was 0.3 ml (range 0.1–1.3 ml) for the proximal occlusion of the target vessel and 0.25 ml for the distal

Table 1. Patient characteristics.

Variable	Mean (range), No. (percentage) $N = 20$
Demographic data	
Age	81 (45–94)
Sex ratio (M/F)	15/5
Comorbidities	
Hypertension	16 (80%)
Diabetes	5 (25%)
Tobacco	6 (30%)
Obesity (BMI $>$ 30 kg/m^2)	1 (5%)
CKD stage 5	3 (15%)
Rutherford stages	
4	8 (40%)
5	7 (35%)
6	5 (25%)

CKD, chronic kidney disease.

Table 2. Operative data.

Variable	Mean ± SD (range) or No. (percentage) $N = 20$
Proximal anastomosis	
SFA	15 (75%)
ATK popliteal artery	5 (25%)
Distal anatomosis	
Anterior tibial artery	5 (25%)
Tibioperonal trunk	3 (15%)
Peroneal artery	6 (30%)
Posterior tibial artery	5 (25%)
Pedal artery	1 (5%)
Anastomosis length (mm)	20.2 ± 8.9 (9–50)
Number of RTP injections	
Proximally	
1	18 (90%)
2	1 (5%)
3	1 (5%)
Distally	
1	19 (95%)
2	1 (5%)
Volume of RTP injected (ml)/patient	
Proximally	0.3 (0.1–1.3)
Distally	0.25 (0.1–0.6)
Duration (min)	
Occlusion	14.4 ± 4.5 (5–22)
Distal anastomosis	13.4 ± 4.3 (7–27)
Bypass procedure	175 ± 49 (94–275)
Quality of bloodless field	
Excellent	8 (40%)
Good	12 (60%)
RTP residual plug on control angiography	2 (10%)

SFA, superficial femoral artery; ATK, above the knee.

occlusion (range 0.1—0.6 ml). Occlusion on the proximal side was achieved in a single injection of RTP in 18 patients (90%). Two patients required a second proximal injection and a third injection was necessary in one of them. Distal vascular occlusion was obtained in a single injection in 19 patients (95%); one patient required a second distal injection. Mean duration of occlusion was 14.4 ± 4.5 min (range 5—22 min). Mean duration of distal anastomosis completion was 13.4 ± 4.3 min (range 7—27 min). Mean anastomosis length was 20.2 ± 8.9 mm (range 9—50 mm). Quality of occlusion was qualified as excellent in eight cases (40%) and good in 12 cases (60%), meaning that no adjunct occlusion device was needed to complete the anastomosis. Mean duration of surgical procedure was 175 ± 49 min (range 94—275 min). Operative data are listed in Table 2.

Routine on-table angiography showed one occluded collateral of the pedal artery in the first patient and an occlusion of the origin of the peroneal artery in the second patient. These occlusions were believed to be the result of residual RTP that had not yet been dissolved. Consequently, we performed in both cases an embolectomy with a 3 French embolectomy catheter (Lemaitre Vascular, Burlington, MA, USA) and flow was restored.

Post-operative outcomes

Mean length of stay was 25.6 ± 13 days (range 11—58 days). Post-operative complications were observed in 10 patients (50%). Seven patients (35%) showed a wound dehiscence, from which only one needed a surgical revision (minor complication). Four patients (20%) suffered from pneumonia and one patient (5%) from myocardial infarct (major complications). The 30-day mortality rate was 10% and one patient died later in the hospital. The cause of death was unrelated to the RTP device but due to pulmonary sepsis in all patients. The 6-month mortality rate was 15%. Mean duration of follow-up was 173 ± 61 days (range 5—250 days). Primary patency rate was 80% at 3 months and 75% at 6 months. Limb salvage rate was 94% at 3 months and 87.5% at 6 months: two patients had a major amputation due to unhealing of major necrotic tissue at the foot level with occluded bypass.

DISCUSSION

Our results suggest that injection of RTP in crural arteries for blood-flow occlusion offers a good bloodless field for anastomotic procedures with no related major adverse events.

RTP has already been described to be safe and effective in achieving a bloodless field in peripheral arterial bypass or arteriovenous fistula for haemodialysis.[17,18] We found that RTP achieved an excellent or good bloodless field in 100% of the cases, which is correlated with previous publications.[17–19] Duration of occlusion is probably limited to 20 min but can be extended when additional injections are used. This is usually enough to perform the anastomosis as occlusions were achieved with a single injection proximally and distally in 92.5% of patients. The occlusion quality of RTP is dependent on some criteria such as quality of the target vessel wall and blood pressure. Indeed, smooth endothelial surface prevents the adherence of RTP to the wall while the presence of calcification or atherosclerotic plaque favours it. In addition, speed of injection and cannula withdrawing are probably also important to get a homogeneous plug without air bubbles inside. High blood pressure in large vessels as in common femoral arteries could also compromise an extended occlusion time. The increase of RTP viscosity could help to avoid these disadvantages and extend the indication such as kidney transplantation.

A noteworthy advantage of the RTP is represented by the limited dissection of the target distal vessel, which is important to decrease the devitalisation of the surrounding soft tissue with potential deep venous network bleeding and damage to collateral arteries. The selected anastomotic area is the only section of the artery that needs to be dissected because no clamps need to be placed at a distance on each side of the arteriotomy. Moreover, the continuous suture is facilitated by the RTP plug, which maintains a cylindrical configuration of the target vessel and can be penetrated by surgical needles.

The dissolution of the plug with cold saline is a critical step of the procedure. Bouchot and colleagues reported the need of a Parsonnet probe to dissolve the plug in 11% (10/91) of coronary bypasses.[19] The residual plug was also described in an anterior tibial artery after an indirect injection of cold saline.[18] We observed two residual occlusions in our first two patients, which were removed with an embolectomy catheter. RTP spontaneous dissolution is a pure physical process due to ‘surface erosion’ of the polymer, which we can speed up with application of cold saline. We think that the residual plugs were seen before they had completely dissolved because we performed the control angiography right after completion of distal anastomosis and that we, in someway, failed the instant dissolution due to inadequate application of cold saline. We analysed these two events and concluded that instant dissolution of RTP requires perforation with the cold saline cannula of the whole plug (Fig. 3). Since we changed this step, no additional adverse events were observed. We also continued to use RTP for femoro-distal bypass surgery after July 2011. As we did not observe any residual plug in the 10 further control angiographies, we do not now perform this examination any more but only rely on backflow bleeding. In our experience, we would not recommend completion of routine on-table angiography when using RTP.

RTP is an alternative device to clamp the vessels with the advantage of avoiding endothelium damage. Preservation of endothelium by RTP could be an important issue with reduction of subsequent intimal hyperplasia. This assumption needs however to be proved and our study was not designed to detect a reduction of a stenosis at the post-anastomotic site.

The limitation of our study is precisely the small number of patients with a short-term follow-up (6 months). Yet the aim of our investigation was to evaluate the technical success rate of the RTP device, before performing a larger

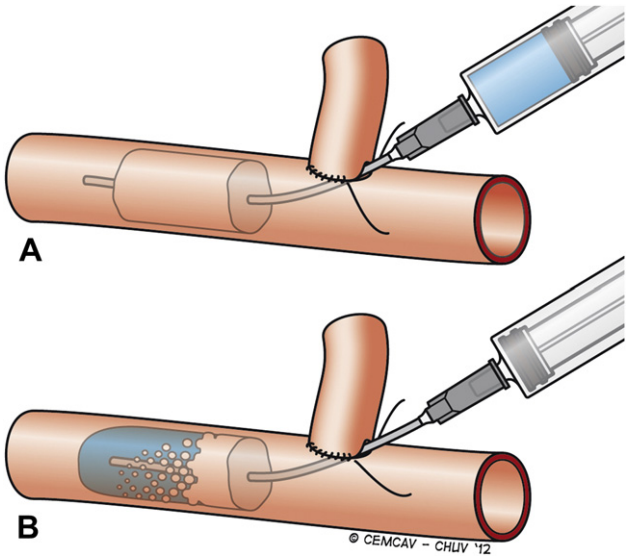

Figure 3. Dissolution of the RTP plug with cold saline. A, the cannula must perforate the whole plug before cold saline is injected. B, the cannula has to be progressively withdrawn as the cold saline is injected and the plug dissolved.

randomised controlled prospective trial. One factual drawback of the device is its cost that represents one and a half times the price of two occlusion catheters.

In conclusion, this study shows that the novel RTP is safe and effective in occluding calcified crural arteries, and allows sufficient time for performing challenging distal anastomoses in patients with CLI. RTP could be less deleterious for endothelium and could therefore contribute to improve patency rate of distal bypass in patients with heavily calcified crural arteries.

ACKNOWLEDGEMENTS

The authors wish to thank Pietro Poglia and Yann Fournier for their assistance in data collection.

CONFLICT OF INTEREST

Pluromed Inc. provided the RTP to the unit at no cost.

The authors had full control of study design, implementation, data analysis, manuscript preparation and received no financial support for the authorship or publication of this article.

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