Institutional report - Coronary

Facilitated anastomosis using a reverse thermo-sensitive polymer for temporary coronary occlusion in off-pump minimally invasive direct coronary artery bypass surgery

Ardawan Julian Rastan*, Thilo Noack, Sreekumar Subramanian, Alpen Nacar, David Holzhey, Volkmar Falk, Friedrich Wilhelm Mohr

Department of Cardiac Surgery, Heart Center, University of Leipzig, Struempellstr. 39, 04289 Leipzig, Germany

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Abstract

To evaluate the safety and efficacy of a novel, reverse thermo-sensitive polymer (LeGoo™) for its ability to provide temporary coronary occlusion and hemostasis during minimally invasive direct coronary artery bypass (MIDCAB) surgery. Between January 2009 and March 2009, 20 consecutive MIDCAB patients were studied. Ten patients received a conventional MIDCAB procedure using proximal vessel loops and CO2 blower (control group). The following 10 patients were operated by an otherwise identical procedure, except that intracoronary administration of LeGoo™ was used instead of vessel snares (LeGoo™ group). Left internal mammary artery (LIMA) bypass flow, peri- and postoperative events and perioperative creatinine kinase-MB fraction (CK-MB) release were prospectively analyzed. CO2-blower use was required in three of 10 of the LeGoo™ patients. Procedural time was identical, with a trend of shorter anastomosis time in the LeGoo™ group (12.3 vs. 10.7 min, P=0.11). LIMA-LAD flow was also not different (control 35.8 vs. LeGoo™ 42.5 ml/min, P=0.541). CK-MB values were not statistically different on postoperative days 1 and 2. However, the level of CK-MB 4 h postoperatively was lower in LeGoo™ patients (18.3±6.1 vs. 13.2±2.9 U/l, P=0.006). No major adverse cerebral or cardiovascular event occurred postoperatively and during follow-up of 317±21 days. Using LeGoo™ to achieve temporary coronary artery occlusion is easier to work with during MIDCAB due to the absence of vessel snares and less need of blowing to eliminate blood from the operative field. There were no negative postoperative events associated with the use of LeGoo™.

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1. Introduction

In off-pump coronary artery bypass (OPCAB) surgery, only perfect stabilization and a bloodless field allow performance of the highest quality of distal coronary anastomosis, comparable to conventional coronary artery bypass grafting (cCABG). Thus, achieving this goal is one of the greatest challenges in OPCAB. Traditional OPCAB techniques like intracoronary shunts, vessel loops, or CO2-blowers are commonly used to control coronary blood flow and obtain a dry anastomotic environment. However, each of these techniques may cause endothelial dysfunction or coronary injury [1–3]. Furthermore, these devices are not always effective to control collateral and retrograde blood flow especially in chronic total vessel occlusions. CO2-blowers are widely used, but excessive blower use may induce graft injury and air embolism, and the blower itself may crowd the anastomotic environment [4]. Additionally, working around an intra-coronary shunt also requires alteration of the needle angles, and sutures may be entangled within vessel loops, making the procedure more difficult. These concerns in standard OPCAB surgery might be the more relevant in situations where surgical access to the anastomotic site is limited by minimally-invasive approaches.

The use of LeGoo™ (Pluromed, Inc, Woburn, MA, USA), a novel reverse thermo-sensitive gel, has previously been shown to be a safe and easily applicable alternative to traditional methods of temporary coronary artery occlusion during OPCAB surgery in animals [5–9]. Recently, the first experiences in humans were reported, finding LeGoo™ to be a safe and highly effective method for temporary flow interruption during OPCAB [10]. The purpose of this study was to evaluate the practicability, safety and efficacy, as well as mid-term outcomes of LeGoo™ during off-pump minimally invasive direct coronary artery bypass (MIDCAB) surgery.

2. Material and methods

2.1. Patients and procedure

At our institution, MIDCAB is a commonly used approach, with a total of 2056 procedures during the past 14 years and at present, approximately 100 procedures per year.
In this study, 20 consecutive patients underwent a MIDCAB procedure from January to March 2009 by one surgeon (A.J.R). In all cases, single bypass of the left anterior descending (LAD) artery was performed using the left internal mammary artery (LIMA). MIDCAB was performed by creating a 6–8 cm left anterolateral thoracotomy through the fourth or fifth intercostal space, single-lung ventilation and a hand-sutured anastomosis of the LIMA to the LAD. The surgical details have been previously described, and were identical in both groups, except for the technique of temporary LAD occlusion [11]. The first 10 consecutive patients served as control, in which a proximal vessel snare was used to compress the LAD and stop antegrade blood flow. No distal vessel snare or intracoronary shunt was used to avoid potential distal vessel damage. In the following 10 consecutive patients, intracoronary administration of LeGoo™ was used to stop antegrade and retrograde blood flow during LIMA-LAD anastomosis. After coronary stab incision, the antegrade blood flow was temporarily controlled by a small surgical swab, followed by completion of the proximal and distal arteriotomy to about a total 5 mm length. Next, 150 μL of LeGoo™ was injected approximately 2 cm proximally and distally into the LAD to allow for a stable plug and the swab was released. In case of repetitive ante- or retrograde oozing, or plug loss, an additional 100 μL were applied. The arteriotomy was then dried using another surgical swab, followed by LIMA-to-LAD anastomosis using a 8-0 polypropylene suture (Fig. 1). Bypass flow to the LAD was quantified by repetitive Doppler flow measurements on the skeletonized LIMA (VeriQ™ system, MediStim, Oslo, Norway).

Patients were routinely transferred to the recovery room and extubated within the first 2 h. The CK enzyme levels were measured 4 h after surgery, and on postoperative days 1 and 2. Telephone follow-up was performed after a mean of 317 ± 21 days and was 100% complete.

2.2. LeGoo™ (Poloxamer 407)

It is a non-toxic, non-absorbed and non-metabolized polymer that is liquid at room temperature and turns to a solid gel at body temperature. Intravascular administration of LeGoo™ results in a vascular plug for several minutes, allowing the surgeon to work in a bloodless field (Fig. 2). It dissolves spontaneously after several minutes or instantly after local application of crushed ice or iced water. Once dissolved below a minimum concentration, the polymer can never re-solidify. LeGoo™ is supplied in pre-filled syringes.
as a sterile, single-use product. Each LeGoo™ kit also contains sterile olive tipped cannulae of different lengths that are fitted to the syringe prior to use. The LeGoo™ syringes are available in multiple volumes, ranging from 250 μl to 10 ml, thereby accommodating a range of vessel sizes and desired plug lengths, but for study indication, we only used 250 μl volumes. LeGoo™ has received the CE mark (Conformité Européenne).

2.3. Statistics

Data were 100% complete. A statistical analysis was performed for preoperative conditions including additive and logistic EuroSCORE, ejection fraction, creatinine and non-elective indication. A statistical analysis was also performed for certain surgical outcomes including anastomosis time, length of surgery, bypass flow, ventilation time, length of hospital stay and MACCE. The t-test was used for continuous variables and a Wilcoxon rank sum was used for ordered variables. Where appropriate, the P-value for certain categorical variables was calculated based on the Fisher’s exact test. The statistical calculations were performed using the 17.0 SPSS and Microsoft Excel 2003 software packages. The study protocol and anonymous data publication was approved by the local Ethics Committee. All MIDCAB patients reported here were excluded from participation in the simultaneously performed randomized clinical trial of LeGoo™ vs. traditional vessel loops.

3. Results

There were no significant differences in baseline and extracardiac morbidity (Table 1). Mean age was 63.1 ± 11.1 years for control vs. 65.2 ± 12.2 years for LeGoo™ patients (P = 0.68). Additive EuroSCORE was 3.1 ± 2.7 in the control patients and 4.0 ± 2.3 in the LeGoo™ group (P = 0.46). There was a significantly higher rate of previous percutaneous coronary interventions on the LAD in the control group (P = 0.02). There were formally more incomplete revascularizations in the LeGoo™ group, since more of these patients were treated within a primary hybrid revascularization strategy, with optional percutaneous coronary intervention (PCI) if myocardial ischemia persisted after MIDCAB.

All 20 patients underwent the MIDCAB procedure successfully, without sternotomy or cardiopulmonary bypass. No intraoperative arrhythmia or significant ischemia was noted during LAD occlusion in either group. Use of CO₂-blower was required in three of 10 of the LeGoo™ patients, compared to its use in all patients of the control group (P < 0.003, Table 2). Procedural time was identical with a trend towards shorter anastomosis time in the LeGoo™ group (12.3 ± 2.6 vs. 10.7 ± 1.5 min, P = 0.11). LeGoo™ subjectively provided better anastomotic site visibility and the surgical field was less crowded in the LeGoo™ patients. In four of 10 LeGoo™ patients, LeGoo™ had to be readministered during anastomosis for proximal (n = 2) and distal (n = 2) coronary reocclusion.

LIMA-LAD bypass flow measurements revealed not significant differences between the groups (control 35.8 ± 19.6 vs. LeGoo™ 42.5 ± 27.8 ml/min, P = 0.541).

| Table 1. Patients’ demographic data | Control | LeGoo™ | P-value |
|------------------------------------|---------|--------|---------|
| **Baselines**                       |         |        |         |
| Age, mean ± S.D.                   | 63.1 ± 11.1 | 65.2 ± 12.2 | 0.68 |
| Male, n                            | 7        | 9      | 0.58   |
| Height, cm                         | 169.8 ± 7.0 | 170.6 ± 6.3 | 0.79 |
| Body weight, kg                    | 76.7 ± 6.0 | 83.4 ± 20.3 | 0.35 |
| Body mass index                    | 26.6 ± 2.7 | 28.5 ± 5.8 | 0.37 |
| Body mass index > 30, %            | 1        | 4      | 0.30   |
| **Extracardiac morbidities**       |         |        |         |
| Diabetes, n                        | 1        | 1      | 1.0    |
| COPD, n                            | 1        | 0      | 1.0    |
| Smoker, n                          | 1        | 0      | 1.0    |
| Peripheral vascular disease, n     | 1        | 0      | 1.0    |
| Hyperlipidemia, n                  | 3        | 4      | 1.0    |
| Arterial hypertension, n           | 9        | 7      | 0.58   |
| Renal insufficiency, n             | 1        | 1      | 1.0    |
| **Additive EuroSCORE**             |         |        |         |
| Control                             | 3.1 ± 2.7 | 4.0 ± 2.3 | 0.46 |
| LeGoo™                              | 3.0 ± 3.0 | 3.8 ± 2.8 | 0.35 |
| **Cardiac morbidities**             |         |        |         |
| Previous cardiac surgery, n        | 1        | 1      | 1.0    |
| Pulmonary hypertension, n          | 0        | 0      | 1.0    |
| Atrial fibrillation, n             | 0        | 2      | 0.47   |
| s/p PM/ICD implantation, n         | 1        | 0      | 1.0    |
| s/p AMI, n                         | 3        | 2      | 1.0    |
| AMI < 21 days before surgery, n    | 2        | 0      | 0.47   |
| s/p PCI, n                         | 7        | 3      | 0.07   |
| Total number of prior PCI, n       | 10       | 3      | 0.06   |
| s/p PCI of the LAD, n              | 7        | 1      | 0.02   |
| LAD occlusion                      | 4        | 1      | 0.30   |
| **Coronary artery disease**        |         |        |         |
| Single-vessel, n                   | 7        | 5      | 0.65   |
| Two-vessel, n                      | 2        | 4      | 0.63   |
| Three-vessel, n                    | 1        | 1      | 1.0    |
| Left main, n                       | 0        | 1      | 1.0    |
| Non-elective indication, n         | 0        | 4      | 0.09   |
| Acute coronary syndrome, n         | 0        | 2      | 0.47   |

Postoperative CK trends are depicted in Fig. 3. The CK-MB levels 4 hours after surgery were significantly lower in the LeGoo™ group than in the control group (LeGoo™ 13.2 ± 2.9 U/l vs. control 18.2 ± 6.1 U/l, P = 0.006). The CK-MB values on POD 1 (LeGoo™ 16.7 vs. control 18.2 U/l) and POD 2 (LeGoo™ 13.8 vs. control 19.7 U/l) were not statistically different between both groups. The difference of total CK release 4 hours postoperatively did not reach statistical significance (LeGoo™ 223 vs. control 124 U/l, P = 0.17). There were no negative postoperative events.

| Table 2. Perioperative results | Control | LeGoo™ | P-value |
|---------------------------------|---------|--------|---------|
| **Intraoperative results**      |         |        |         |
| Anastomosis time, minutes       | 12.3 ± 2.6 | 10.7 ± 1.5 | 0.11 |
| Length of surgery, minutes      | 116.9 ± 13.6 | 116.8 ± 16.4 | 0.90 |
| Use of proximal LAD snare, n    | 10       | 1      | < 0.001 |
| Use of CO₂ blower, n            | 10       | 3      | 0.003   |
| Incomplete revascularization, n | 1        | 4      | 0.30    |
| Conversion to sternotomy, n     | 0        | 0      | 1.0     |

LAD, left anterior descending; COPD, chronic obstructive pulmonary disease; PM/ICD, pacemaker and implantable cardioverter/defibrillator; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention s/p status post; CK-MB, creatinine kinase, MB fraction.
OPCAB and MIDCAB are well-established techniques for CABG, and incremental improvements in coronary stabilization and instrumentation have produced equivalent or superior results compared to cCABG in many centers worldwide. In recent years, efforts have been made to facilitate the distal anastomotic process using automated distal anastomotic devices, which have not gained general acceptance and marketability [12]. However, many techniques are currently used to achieve a bloodless field, indicating the lack of a single, optimal technique. In recent studies, the poloxamer 407 (Pluromed Inc, Woburn, MA, USA) has shown promise as a means of achieving temporary coronary occlusion without causing endothelial dysfunction or compromising patency [6–10]. During these studies, LeGoo™ has been shown to be not only a good alternative to the aforementioned techniques of extra- and intracoronary occlusion devices (which have all a potential for tissue injury and incomplete occlusion), but also was easily and safely applicable.

Marketed under the trade name LeGoo™, poloxamer 407 is a non-thrombogenic gel that is biocompatible with cells and body fluids [5, 13]. Based on extensive laboratory and animal studies, LeGoo™ is known to form a gel plug that conforms to the vascular wall, and can either dissolve spontaneously after several minutes or be dissolved easily and rapidly with ice or cold liquids when required. These reverse thermo-sensitive properties make it particularly attractive for controlled vascular occlusion. Furthermore, physical dissolution of LeGoo™ does not result in metabolic byproducts.

The lack of clamps, vessel loops and a mister-blower apparatus render the operative field relatively unobstructed, which is of particular importance in MIDCAB operations. Furthermore, a partially bloodless field often requires more regional ischemic time to complete the anastomosis, since blood must be intermittently sucked or blown away, and this is counterproductive to procedural efficiency. In contrast to conventional techniques of coronary occlusion, LeGoo™ may be injected distal to the arteriotomy to eliminate retrograde flow and improve visualization. Furthermore, unlike an indwelling coronary shunt, the transparent gel plug may also be sutured into the anastomosis since it will dissolve later. In our opinion, these qualities have substantial benefits over traditional coronary occlusion techniques, and make this product a valuable adjunct to OPCAB and MIDCAB operations.

Recently, Manchio et al. investigated the utility of LeGoo™ in a rat femoral artery model, and concluded that it showed promise for its ability to allow for hemostasis while performing microvascular anastomoses [14]. Furthermore, they noted that improvements were made with regard to injection techniques, appropriate volumes, ability to reliably determine gel plug dissolution, and final vessel patency. Aside from the construction of anastomoses, selective occlusion of vessels may be useful to accomplish bloodless surgical resections. Moinzadeh et al. recently reported a reliable angiographic delivery technique for LeGoo-XL™ that allowed for selective angiographic occlusion of the renal lower pole segmental artery [15]. Subsequent lower pole robotic partial nephrectomies were completed with minimal blood loss.
Furthermore, since LeGoo™’s physical state may be easily modulated, ischemia and reperfusion can be finely controlled, thereby extending the utility of this product to the realm of ischemia-reperfusion injury. Ischemic pre-conditioning and controlled reperfusion through partial dissolution of LeGoo™ may be of therapeutic benefit in a wide range of medical and surgical conditions.

In conclusion, LeGoo™ is a safe and effective means of achieving temporary coronary artery occlusion. Since it renders the operative field free of intra-coronary shunts, CO2 mister-blowers, and vascular snares, it is particularly attractive in MIDCAB operations. It is potentially superior to conventional techniques not only because injection of the gel distal to the arteriotomy prevents retrograde flow and improves visualization, but also because sutures may be passed through the gel plug during anastomotic construction. Further and larger studies, like the ongoing randomized clinical trial in OPCAB surgery, are required to determine the impact of LeGoo™ on blood loss, procedural times and major adverse events, including long-term bypass patency, prior to widespread implementation.

5. Limitations

The usual limitations of a small, non-randomized prove-of-concept study are applicable. Angiographic confirmation of LIMA-LAD patency and long-term outcome were not considered in this study.

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