

Randomized Clinical Trial Comparing a Thermosensitive Polymer (LeGoo) With Conventional Vessel Loops for Temporary Coronary Artery Occlusion During Off-Pump Coronary Artery Bypass Surgery

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Background. During off-pump coronary artery bypass graft (OPCABG) surgery, a bloodless surgical field is mandatory for visualization and construction of optimal coronary anastomoses. Presently used temporary vascular occluders are known to cause endothelial dysfunction and vessel injury. The present prospective multicenter randomized clinical trial evaluates safety and efficacy of a novel thermosensitive polymer (LeGoo) as an atraumatic temporary vascular occluder.

Methods. Between July 2008 and February 2010, 110 patients undergoing OPCABG were randomized between LeGoo (LG) and conventional vessel loops (VL) for coronary artery occlusion during construction of the distal anastomosis. A semiquantitative 4-point scale was used to evaluate the degree of bloodless surgical field and surgical comfort. Duration of coronary artery occlusion was also recorded. Safety during the operation and ensuing 30 days was evaluated by a composite endpoint of major adverse cardiac events that consisted of death from all causes, graft occlusion, myocardial infarction, and low cardiac output.

Results. Fifty-six patients (117 distal anastomoses) were randomly assigned to LG and 54 patients (122 anastomoses) to VL. There were 2 anastomoses crossed

over from LG to the control arm, and 3 from control to LG. Five anastomoses in LG patients were treated with an alternative device (shunts). Satisfactory hemostasis was achieved in 88.0% of LG anastomoses (103 of 117) compared with 60.7% of VL anastomoses (74 of 122; $p < 0.001$). Mean total anastomotic time was 12.8 minutes in the LG group and 15.1 minutes in the VL group ($p < 0.001$). This difference was more pronounced for arteries on the posterior and lateral than on the anterior walls of the heart. Composite adverse events were similar in the two groups: 3 of 48 LG patients and 3 of 46 VL patients. There was 1 death in the LG group. One patient in the LG group and 1 in the VL arm had a myocardial infarction. No operation was converted from OPCABG to CABG with cardiopulmonary bypass.

Conclusions. LeGoo is a safe and effective temporary coronary occluder during OPCABG. It provided a dry surgical field for visualization of the anastomotic field and surgical comfort more frequently than conventional vessel loops. In addition, anastomotic times were shorter with LG. Major cardiac adverse events were similar in the LG and VL arms.

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There is considerable debate about the superiority of off-pump coronary artery bypass graft (OPCABG) surgery over conventional on-pump CABG surgery [1, 2]. Evidence is growing that certain high-risk patient subgroups benefit from avoiding cardiopulmonary bypass

(CPB) and cardioplegic arrest [3–6]. Optimal visualization for working in a bloodless field is mandatory in OPCABG for crafting a high-quality coronary anastomosis. Conventional extravascular and intravascular temporary coronary occlusive devices used during OPCABG include intracoronary shunts, clamps, vessel loops, and snares with or without the addition of CO₂ blowers. Unfortunately, these techniques may cause endothelial dysfunction or coronary wall injury [7–9] and are not always effective in controlling collateral and retrograde

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coronary blood flow, especially in the face of total coronary occlusion. Moreover, intracoronary shunts crowd the operative field and may interfere with placement of sutures, making the procedure unnecessarily difficult [10]. In addition, CO₂ blowers may cause coronary vascular dissection or air embolism.

LeGoo (Pluromed, Woburn, MA) is a novel reverse thermosensitive gel. Animal studies demonstrated that it is safe, easy to apply, and an effective alternative to traditional methods of temporary coronary artery occlusion during OPCABG surgery [11–15]. Recent clinical experience in humans also indicates that LeGoo is safe and highly effective for temporary flow interruption during OPCABG and minimally invasive direct CABG surgery [16–18]. A randomized clinical trial was lacking, however. The purpose of this prospective randomized clinical trial was to compare feasibility, safety, and efficacy of LeGoo to conventional vessel loops in obtaining a bloodless anastomotic field during OPCABG. The study hypothesis postulated that LeGoo provides a bloodless surgical field in a larger proportion of anastomoses than conventional temporary occluders.

Material and Methods

Between July 2008 and February 2010, a total 110 patients undergoing OPCABG surgery were randomized in a 1:1 ratio between LeGoo (LG) and vessel loops (VL) for temporary coronary artery occlusion at nine study centers in Europe and Canada. Elective operations with at least one 70% proximal coronary stenosis greater than 70% and an age of 18 to 79 years were included. Exclusion criteria were left ventricular ejection fraction less than 40%, left main coronary stenosis greater than 50%, previous cardiac surgery, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) more than 10, urgent or emergent surgery, forced expiratory volume in 1 second (FEV₁) less than 45% of predicted, intramyocardial coronary arteries, plasma creatinine greater than 200 μmol/L and plasma bilirubin greater than 21 μmol/L. An Institutional Review Board at each site approved the protocol, and all patients provided written informed consent, consistent with the Declaration of Helsinki, the International Conference on Harmonisation, and all local regulations.

LeGoo is a nontoxic, nonabsorbed, and nonmetabolized polymer that is a viscous liquid at room temperature and transits to a solid gel instantaneously when exposed to body temperatures [21]. Intravascular administration of LeGoo produces a firm gel plug that lasts a number of minutes, allowing work in a bloodless field [11–18]. The gel dissolves spontaneously after minutes or, when desired, instantaneously by topical application of crushed ice or iced saline. Once dissolved below a minimum concentration, the polymer does not resolidify and is excreted unmetabolized from the body.

LeGoo is supplied in prefilled syringes as a sterile, single-use product available in volumes ranging from 250 μL to 10 mL, to accommodate a range of vessel sizes and desired plug lengths. Each LeGoo kit also contains spe-

cially designed sterile, soft olive-tipped cannula of various diameters and lengths to fit different size vessels and reach coronary arteries at different locations on the heart. Before use, the appropriate sized cannula is attached to the LeGoo syringe. LeGoo received the CE (Conformité Européenne) mark.

In the present study, LeGoo was administered in the beating heart by temporarily occluding blood flow in the target coronary of a beating heart with a small surgical swab placed proximal to the intended site of anastomosis. A stab wound was made at the desired location in the coronary artery, followed by completion of the arteriotomy. Appropriate sized cannulas were inserted proximally and distally for LeGoo administration through the arteriotomy for a distance of approximately 2 cm. LeGoo was injected, and the occlusive surgical swab was removed once the newly formed firm gel plugs stopped blood flow into the field. In cases of inadequate initial hemostasis or resumption of bleeding into the anastomotic field due to dissolution of the polymer plug, additional LeGoo was administered.

In the control group, proximal snares or vessel loops were used to control bleeding into the arteriotomy. Distal vessel snares were applied when necessary but are usually not recommended to avoid potential vessel damage. Carbon dioxide blowers were employed at the discretion of the operating surgeon. It was required that surgeons have experience with the use of LeGoo in at least five OPCABG operations before participating in the study.

The primary study endpoint was based on the hemostasis in the anastomotic field using the following 4-point semiquantitative scale: 1 = excellent hemostasis, no bleeding into operative field; 2 = good hemostasis, minimal bleeding into operative field that does not interfere with suturing; 3 = fair hemostasis, modest bleeding into the operative field requiring intermittent use of another device to control bleeding; and 4 = poor hemostasis, copious bleeding into the operative field requiring continuous use of another device to control bleeding. Hemostasis was considered satisfactory at levels 1 or 2 on this scale. Levels 3 and 4 were regarded as unacceptable bleeding into the field manifested by the need for CO₂ blowers, intracoronary shunts, or other occluders.

Secondary efficacy endpoints consisted of the time required from beginning preparation of the anastomotic site to the point vessel occlusion was achieved, the total duration of crafting the anastomosis, the number of blood or blood product units transfused during hospitalization, and the difference between preoperative and discharge hemoglobin values.

The primary safety endpoint was expressed in terms of a composite of four major adverse cardiac events (MACE): (1) death from all causes, (2) graft occlusion, (3) low cardiac output syndrome, and (4) myocardial infarction intraoperatively and up to the 30-day follow-up visit. The definition of myocardial infarction was based on the SYNTAX study definition and in accordance with the early European Society of Cardiology postoperative CABG type V universal definition of myocardial infarction [19, 20].

Statistical Analysis

Analyses were conducted using SAS system software, version 9.2 (SAS Institute, Cary, NC). Randomization was performed in a 1:1 fashion, stratified by study center, using variable block sizes. The study was powered to test the null hypothesis of inferiority, against the one-sided alternative hypothesis of noninferiority in the rates of satisfactory hemostasis between the LeGoo and control groups, using a 10% noninferiority margin. A test of superiority in these rates was to be performed if the null hypothesis of inferiority was rejected. The significance level for this test was set at 0.0245 (one sided), to account for a single interim analysis at the midpoint of the trial. The sole prespecified purpose of the interim analysis was to reestimate the sample size requirements, as no prior data were available to estimate the expected rate of successful hemostasis for the LeGoo group during study planning. The interim analysis showed that no increase in the original planned sample size was required.

Continuous variables were described using mean \pm SD, and discrete variables were reported as counts and percentages. For outcomes measured per anastomosis, a generalized estimating equation model was fit, in order to take into account the correlation of the repeated measures within patients. An identity link was used for continuous outcomes (applying transformations as necessary to meet model assumptions), and a logistic generalized estimating equation model was fit to the binary outcome. All other variables were analyzed using the *t* test or Wilcoxon rank sum test for continuous and ordered variables, and χ^2 or Fisher's exact test for discrete outcomes. Analysis was performed on an intention-to-treat as well as an as-treated basis. A probability of less than 0.05 was considered significant for all hypothesis tests other than primary effectiveness. All reported *p* values are two-sided. Missing values were not replaced by imputed values.

Results

Fifty-five patients were randomly assigned to the LeGoo arm and 55 to the control arm. Patient demography, cardiac and extracardiac characteristics, and pattern of coronary artery disease were similar (Table 1). Coronary artery size, severity of stenosis, grafted arteries, and conduits used were also similar in the two arms of the trial (Table 2).

Administration of LeGoo proved simple and safe. The learning curve was short. Injection of LeGoo took seconds and the polymer turned into a firm gel immediately after injection. Blood flow into the anastomotic field stopped simultaneously. No adverse events were associated with injection of LeGoo. The time required to apply the occlusive device on the coronary arteries and total duration of anastomosis were significantly longer in the VL arm than in the LG arm (Table 2). This difference was more pronounced for arteries on the posterior and lateral than on the anterior walls of the heart, indicating that LeGoo is especially advantageous in difficult access ar-

Table 1. Baseline Characteristics of the LeGoo Off-Pump Coronary Artery Bypass Graft Surgery Study Population

Characteristic	LeGoo n = 56	Control n = 54	<i>p</i> Value
Extracardiac variables			
Age, years	63.7 \pm 9.9	64.4 \pm 8.3	0.7
Female, %	19.6	14.8	0.6
Diabetes mellitus, %	28.6	16.7	0.2
COPD, %	3.6	9.3	0.3
Peripheral vascular disease, %	12.5	25.9	0.09
Body mass index	28.8 \pm 3.9	28.0 \pm 4.1	0.3
Cardiac profile			
LV ejection fraction, %	61.3 \pm 11.2	60.5 \pm 9.1	0.7
NYHA class II-IV	60.7	63.0	0.8
CCS class II-IV	82.1	87.0	0.6
Previous myocardial infarction, %	12.5	7.4	0.5
Abnormal Q wave in preoperative ECG, %	19.6	9.3	0.2
Atrial fibrillation, %	5.4	7.4	0.7
Preoperative antiplatelet medication, %	78.6	83.3	0.6
Pulmonary arterial hypertension, %	3.6	11.1	0.2
Systemic hypertension, %	78.6	75.9	0.8
Laboratory values			
Plasma creatinine, μ mol/L	85.6 \pm 20.5	82.6 \pm 18.5	0.4
Plasma bilirubin I, μ mol/L	10.8 \pm 5.8	10.1 \pm 5.1	0.5
Hemoglobin, g/dL	13.5 \pm 2.0	13.8 \pm 1.8	0.5
Extent of coronary involvement, %			
One-vessel disease	25.0	20.4	
Two-vessel disease	30.4	27.8	
Three-vessel disease	44.6	50.0	
Four-vessel disease	0	1.9	
Status post-PCI/stent	30.4	29.6	0.9
Logistic EuroSCORE, %	2.3 \pm 1.8	2.5 \pm 1.5	0.1

CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

eas, as already observed during minimally invasive direct CABG [18].

The semiquantitative 4-point scale used for analyzing quality of hemostasis during performance of the anastomosis revealed that quality of bloodless field was satisfactory in a significantly higher percentage of the LG group than VL group (Table 2). There were 2 anastomoses crossed over from LeGoo to the control arm and 3 from control to LeGoo. Five anastomoses in LG patients were treated with an alternative device (shunts). Total anastomosis times were greater on the posterior and lateral wall of the heart with VL but not with LG (Table 2).

Table 2. Coronary Pathology and Bypass Grafting

Coronary and Graft Details	Coronary Anastomoses		p Value
	LeGoo n = 121	Control n = 127	
Distribution of vessel size, %			0.20
1–2 mm	71.1	63.0	
2–3 mm	26.4	33.9	
>3 mm	2.5	3.1	
Degree of vessel stenosis, %			0.14
>50%	6.6	9.4	
>70%	58.7	43.3	
>90%	34.7	47.2	
Grafted vessel, %			0.50
LAD	42.1	40.2	
Diagonal	13.2	13.4	
Marginal	14.8	18.1	
Circumflex	5.0	3.1	
RCA	8.3	14.2	
PDA	5.0	5.5	
Others	11.6	5.5	
Grafts, %			0.70
LIMA	56.3	48.8	
RIMA	14.3	15.0	
Saphenous vein	24.4	29.9	
Radial artery	5.0	6.3	
Details of anastomoses			
End-to-side, %	85.1	89.8	0.30
Side to side, %	14.9	11.2	
Time needed to occlude vessel, minutes (median)	1.8	4.6	<0.001
Duration of anastomosis, total, minutes	12.8 ± 4.7	15.4 ± 6.1	<0.001
To LAD/diagonal territory, minutes	12.9 ± 4.9	14.4 ± 5.3	
To marginal/circumflex territory, minutes	12.2 ± 3.7	16.1 ± 5.6	
To RCA/PDA territory, minutes	13.8 ± 6.1	17.6 ± 8.2	
Bloodless field satisfactory, levels 1 and 2 (number of anastomoses)	88% (103/117)	60.7% (74/122)	<0.0001
	Patients n = 56	Patients n = 54	
Number of anastomoses/patient	2.3 ± 1.0	2.3 ± 0.9	0.90
Duration of surgery, minutes	180 ± 55	164 ± 41	0.08
Postprocedural hospital stay, days	8.6 ± 4.7	8.0 ± 3.7	0.50

All data and percentages are given on an as-treated basis.

LAD = left anterior descending artery; LIMA = left internal mammary artery; PDA = posterior descending artery; RCA = right coronary artery; RIMA = right internal mammary artery.

Preoperative and discharge hemoglobin values and the number of units of blood transfused during the hospital stay were similar in the two groups: -3.2 ± 1.7 for LG versus -3.1 ± 1.9 for VL ($p = 0.9$), and 0.6 ± 1.6 (median 0) versus 0.7 ± 1.8 (median 0), respectively.

One-month follow-up was 95% for LeGoo patients (53 of 56) and 96% for controls (52 of 54). The composite 30-day safety endpoint (MACE) showed no differences between LG and VL (Table 3).

One patient in the LeGoo group died of severe postoperative coagulopathy. Occlusion of all grafts in that patient resulted in an irreversible low cardiac output syndrome. Two additional patients in the LeGoo-group had graft occlusions (one to a severely diseased 1 mm

artery, and the other had a twisted conduit). There was no graft occlusion in the control arm. One patient in each group had a perioperative myocardial infarction.

Atrial fibrillation was observed in 25.0% of the patients in the LeGoo group and in 14.8% of the controls ($p =$ not significant). Other cardiac- and noncardiac-related complications were similar in the two groups (Table 4).

Comment

This randomized clinical trial demonstrates that LeGoo, a novel reverse thermosensitive polymer, is safe and more effective than conventional vessel loops in achieving a

Table 3. Composite 30-Day Safety Endpoint

Safety Components (MACE)	LeGoo Patients		Control Patients		p Value
	N	%	n	%	
Death-All causes	1/55	1.8	0/51	0	ns
Graft occlusion	3/55	5.5	0/51	0	ns
Low cardiac output	1/55	1.8	2/51	3.9	ns
Myocardial infarction	1/55	2.1	1/46	2.2	ns
Composite safety endpoint	3/48	6.3	3/46	6.5	0.0425

The prespecified safety research hypothesis was that LeGoo would not be worse than control by more than 10%, with 95% confidence. The null and alternative hypotheses were: $\pi_H: \pi_L - \pi_c \geq 0.10$, versus $H_a: \pi_L - \pi_c < 0.10$, where π_L represents the safety composite event rate for LeGoo and π_c the rate for control. The p value associated with this hypothesis test is 0.0425. Hence, noninferiority with a delta of 10% is established.

MACE = major adverse cardiac event; ns = not significant.

bloodless anastomotic field during performance of OPCABG surgery.

Off-pump CABG is a well-established technique for CABG surgery in many centers worldwide because of growing evidence that subgroups of high-risk patients benefit from avoiding cardiopulmonary bypass and cardioplegic arrest [3-6].

A variety of temporary coronary artery occluders are currently in use to achieve a bloodless field, but each has shortcomings and none enjoys universal acceptance. Clamps, shunts, and vessel loops cause endothelial or vessel wall damage. Loops or snares can also injure the

myocardium during placement, resulting on rare occasion in serious bleeding [7]. Intracoronary shunts may injure endothelium and induce endothelial dysfunction. Moreover, the presence of the device crowds the operative field and may render suturing cumbersome [8, 9]. Nonetheless, shunts are frequently employed in an effort to avoid the risk of regional ischemia associated with occlusive devices. Agostini [16] showed that LeGoo can be used to seal the space between shunt and vessel wall to obtain a bloodless field, facilitating the use of smaller shunts that are less likely to damage the endothelium. Carbon dioxide blowers must be used with caution as they can dissect the coronary and also produce air embolism [10]. Finally, several mechanical anastomotic devices have also been developed, but have not gained general acceptance for a variety of reasons.

LeGoo is nonthrombogenic and biocompatible. It is not absorbed or metabolized but breaks up into its physical components and is excreted from the body [21]. LeGoo is derived from a poloxamer through a proprietary fractionation process designed to yield the rapid phase change required to function effectively as a temporary vascular plug. The firm gel plug formed from LeGoo conforms to the contour of the vessel wall even in the presence of atherosclerotic disfiguration. The plug dissolves spontaneously after a number of minutes. When desired, LeGoo can be dissolved instantaneously by application of ice or cold saline [11-15, 21].

In extensive animal studies, LeGoo has proven safe and effective as a temporary atraumatic coronary occluder [11-18]. In addition, Manchio and colleagues [22] used LeGoo in rat femoral arteries and concluded that the polymer showed promise to achieve hemostasis during microvascular anastomoses.

In experimental animals, selective vessel occlusion by LeGoo facilitates bloodless partial resection of solid organs. For this objective Moinzadeh and coworkers [23] developed an angiographic delivery technique for selective occlusion of a branch renal artery that supplies the lower pole segment by LeGoo-XL, now called Lumagel. Using this technique, robotically assisted partial nephrectomies were performed in animals with minimal blood loss.

Table 4. Postoperative Complications

Safety Elements	LeGoo Patients n = 56		Control Patients n = 54		p Value
	n	%	n	%	
Surgical					
Postoperative bleeding	0	0	1	1.9	0.5
Hemorrhage, from graft	0	0	1	1.9	0.5
Wound infection	2	3.6	1	1.9	>0.9
Cardiac					
Atrial fibrillation	14	25.0	8	14.8	0.2
Atrial flutter	1	1.8	0	0	>0.9
AV block >1st degree	0	0	2	3.7	0.2
Cardiac arrest	1	1.8	0	0	>0.9
Cardiac tamponade	0	0	1	1.9	0.5
Pericardial effusion	2	3.6	2	3.7	>0.9
Cerebrovascular accident	1	1.8	0	0	
Pulmonary					
Pneumonia	0	0	1	1.9	0.5
Atelectasis	2	3.6	4	7.4	0.4
Pleural effusion	9	16.1	9	16.7	>0.9
Pneumothorax	1	1.8	0	0	>0.9
Others					
Paralytic ileus	1	1.8	0	0	>0.9
Acute renal failure	1	1.8	1	1.9	>0.9
Urinary tract infection	2	3.6	0	0	0.5

AV = atrioventricular.

Bouchot and colleagues [17] reported on the use of LeGoo in humans as a temporary coronary artery occluder during elective OPCABG in 50 patients with 99 distal coronary anastomoses. The method provided satisfactory bloodless field in 91% of the anastomoses. The average duration of occlusion was 10.5 ± 2.2 minutes. LeGoo proved safe in these patients without device-related adverse events, namely, instances of coagulopathy, metabolic derangements, evidence of distal LeGoo embolization, and so forth. Repeat injection of LeGoo was necessary in approximately one third of the patients either because the injected gel was too cold or because insufficient volume was used to produce a plug of required length. Inadequate plug length may be encountered in patients with diffuse distal disease, severe kinking of the left anterior descending artery, and with arteriotomies close to a high-grade stenosis. In 1 patient ventricular fibrillation was observed after a 4-minute coronary occlusion period by LeGoo. The LeGoo plug was dissolved immediately by application of cold liquid, an intracoronary shunt was inserted, and nonsinus rhythm returned.

Rastan and associates [18] used LeGoo in 10 consecutive patients during minimally invasive direct coronary artery bypass surgery. Visibility was excellent, and the field was less crowded with LeGoo than with conventional devices.

The present randomized clinical trial supports previous observations during extensive animal experimentation and during limited clinical experience with OPCABG surgery about the advantages of LeGoo as a safe atraumatic temporary vascular occluder. It has to be mentioned that 1 patient of the LeGoo group was found with all vessels occluded. Since this triggered a safety discussion, extensive blood analyses were performed in this patient, and a rare hereditary coagulopathy was found. LeGoo proved easy to apply and superior to conventional vessel loop in obtaining bloodless operative field. It appears especially advantageous over conventional devices for inferior and lateral walls of the heart and for arteries that were previously stented, heavily diseased and fragile, completely occluded, and those having large collateral flows.

Study Limitations

Owing to the texture of the investigated device, it was only possible to perform the study in an unblinded fashion. Angiographic confirmation of graft patency and long-term outcome were not considered in this study. Because of the limited number of patients and anastomoses, the study size might have been too small to detect minor differences in bypass function.

In conclusion, LeGoo proved a safe and superior alternative to vessel loop in this randomized clinical trial on OPCABG surgery comparing LG with VL. Adverse event rates and blood transfusion rates were similar in the study and control arms. LeGoo provided a bloodless surgical field that allowed superior visibility and avoided clutter by surgical instruments.

Preferential indications for the use of the thermosensitive gel over conventional devices include stented coronary arteries, fragile and diffusely diseased vessels, large retrograde blood flow into the anastomotic field, and arteries on posterior, lateral, and inferior surfaces of the heart. LeGoo might also be indicated for CABG patients with cumbersome coronary blood flow into anastomotic field in spite effective cardioplegic arrest.

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