Original Article

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Bare Metal Stents Can Maintain Arterial Patency in Traumatic Occlusion

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Background: The standard approach to an occlusive vascular injury is open arterial reconstruction, although endovascular stenting is becoming more common, despite limited evidence. The aim of this study is to examine whether bare-metal stents can be effective in an ovine model of occlusive arterial trauma.
Methods: Through a groin incision, a 2-cm segment of the left superficial femoral artery (SFA) was bluntly injured using a hemostat and injection of air to achieve thrombosis. Animals then underwent a stent deployment (stent group, $n = 5$) or no-treatment (control group, $n = 5$). In the stent group, recanalization of the thrombotic lesion, thromboaspiration, and bare-metal stent deployment were performed. Enoxaparin 1.5 mg/kg was given to all animals. The stent group animals were fed clopidogrel 75 mg and aspirin 125 mg daily. Angiography and Doppler ultrasound were used to evaluate arterial patency during the 7-day observation period.
Results: A thrombosis was obtained in all cases. After a fall in the systolic velocity (SV, cm/sec) in both the control (43 (36–56) to 6 (0–16); $P < 0.001$) and stent groups (45 (32–53) to 8 (0–12); $P < 0.001$), stent implantation resulted in a significant permanent increase of the SV. Day 7 angiography confirmed SFA patency in all (5/5) stented animals, with persisting occlusions in the control group ($P = 0.008$). There was no evidence of distal emboli in the run-off arteries.
Conclusions: Bare-metal stent implantation restores arterial patency of a traumatic occlusive lesion in a standardized ovine model with a short follow-up period.

Keywords: *Arterial Trauma; Trauma Surgery; Endovascular Trauma Management; Bare-Metal Stent; Vascular Surgery*

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INTRODUCTION

Vascular injury represents a significant source of mortality and morbidity in trauma patients [1]. Arterial injury can present as hemorrhage, pseudoaneurysm formation, dissection or occlusion. Hemorrhagic lesions can often be very dramatic, with exsanguination constituting a major cause of potentially preventable death [2]. Occlusive lesions, while less dramatic, affect one-in-five patients with arterial injury and can lead to significant morbidity without prompt reperfusion [3,4].

The mainstay of contemporary management is with operative repair using an interposition or bypass graft in threatened limbs [5]. Endovascular intervention offers another method with which to assess and treat arterial injury. The advantage of such an approach is less invasiveness and relatively easy access to anatomical regions that are challenging to approach via open surgery [6]. This has resulted in a substantial increase in the use of endovascular intervention in arterial trauma; however, this has mainly been done on an impromptu basis and does not have a strong evidence base [3,4,7].

The current experience of traumatic arterial occlusion leans toward the use of covered nitinol stent-grafts to restore patency [8]. The alternative is the use of bare-metal balloon-expandable stents, which has not been evaluated in this context previously. The aim of this pilot study is to examine whether bare-metal stents can be effective in an ovine model of occlusive arterial trauma.

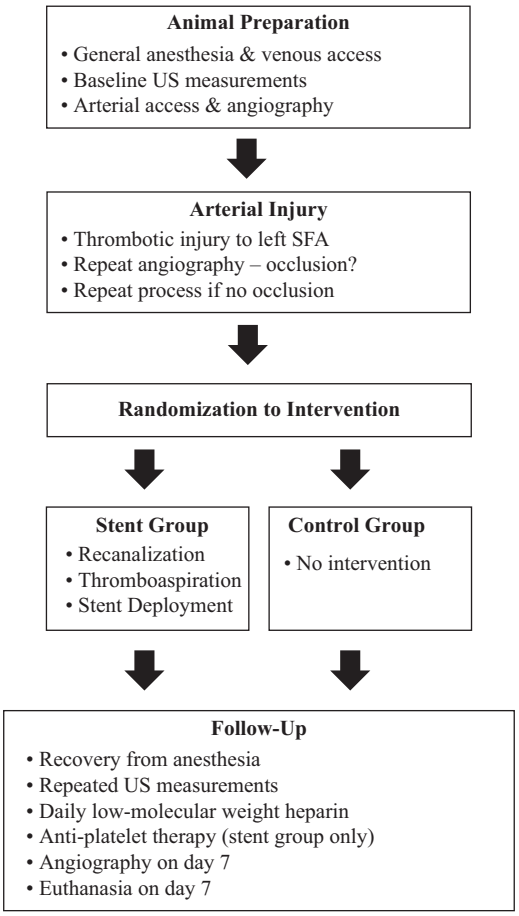

Figure 1 Overview of the experimental protocol.

MATERIALS AND METHODS

Overview

Experiments were carried out in an accredited specialized animal research laboratory under the supervision of veterinary staff. Approval for the study was obtained from the local institutional ethics committee of the Kirov Military Medical Academy (protocol no. 163, approved June 30, 2015). All work was carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

The study utilized female, non-pregnant North Caucasus sheep, weighing between 35 and 45 kg. Sheep were housed in quarantine at the animal facility for 7 days to ensure good health and permit acclimatization. Prior to enrollment in the study protocol, animals were fasted for 36 hours, with free access to water. The study comprised a four-stage protocol consisting of preparation, injury, intervention (stent or control) and follow-up phases (Figure 1).

Animal Preparation

General anesthesia was induced using an intramuscular injection of tiletamine and zolazepam (Zoletil®; Virbac, Carros, France) at a dose of 10 mg/kg. A 1.5 mg intravenous (IV) injection of atropine was also administered to reduce salivation and help facilitate orotracheal intubation. Anesthesia was maintained using inhaled isoflurane at 1–2% concentration. Animals were placed on a radiolucent operating room table in dorsal recumbency. An orogastric tube was inserted for the administration of medication. A 6 French (Fr) sheath was placed into an external jugular vein for drug and fluid delivery. Maintenance fluid (Sterofundin, B. Braun, Germany) was administered at a rate of 3–4 mL per minute during surgical procedures using an infusion pump.

Both groins were prepared with an alcohol solution and draped. Ultrasonography (US) was used to collect baseline measurements of the left and right superficial femoral arteries (SFA). Measurements were made using the linear transducer (10-5 MHz) of a MicroMaxx® Ultrasound System (Sonosite Inc., Bothell, WA, USA). US was then used to guide the retrograde cannulation of the right SFA between its middle and distal third. A 6 Fr sheath was then inserted over a wire into the vessel, which was used for endovascular access, continuous blood pressure monitoring, and blood sampling.

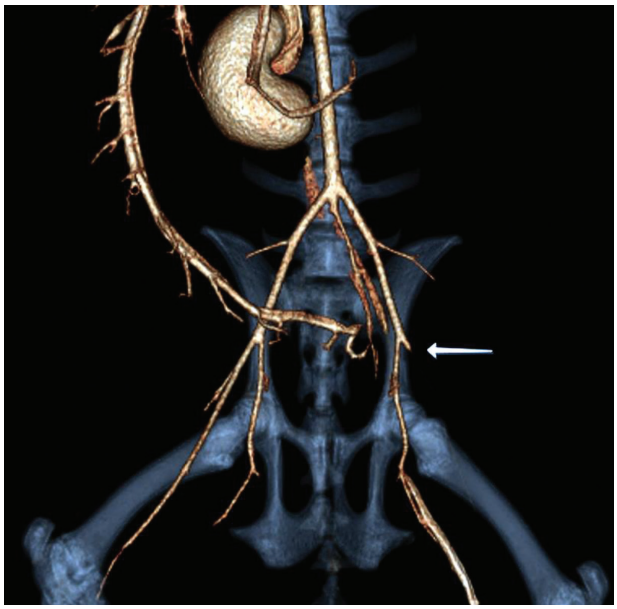

Figure 2 Computed tomography (CT) angiography of the injured left superficial femoral artery demonstrating a sharp cut-off (arrow).

Following baseline blood sampling, catheter angiography of the left-sided extremity was accomplished through the right arterial sheath. A 0.035" wire and a 5 Fr multipurpose small (MPS) catheter (Cordis Endovascular, USA) were used to cross over the aortic bifurcation and to cannulate the orifice of the left iliac artery. An iodine contrast agent Iopamidol 300 mg I/mL (Scanlux, Sanchemia Pharmazeutika AG, Austria) was used in an equal mixture with 0.9% saline for angiography. Images were captured using a mobile fluoroscopy unit or "C-Arm" (SM-20HF, Listem Corporation, Republic of Korea).

Arterial Injury

This injury model has been previously described in detail [9]. Briefly, a 2-cm segment of the left SFA is exposed through a 5–7 cm incision in the groin crease. Proximal and distal control is established and the arterial segment traumatized by repeated clamping and un-clamping of a hemostat. Air (0.5 cc) was injected into the lumen and then aspirated after one hour. Finally, the clamps were removed to restore inline blood flow.

Repeat angiography was then performed via the right groin to assess the lesion. If this demonstrated a complete occlusion, the groin incision was closed with interrupted sutures and post-injury US measurements taken. If flow was observed across the lesion, the lesion was controlled for a further 30 minutes and another cycle of clamp trauma performed. Figure 2 presents a CT angiogram of a characteristic occluding lesion produced by this method.

Following the demonstration of an occluding lesion, animals were ventilated for 60 minutes, simulating the time from injury to treatment. Animals were then randomly allocated to one of two groups: animals undergoing revascularization with a bare-metal stent (stent group, $n = 5$) or a control group undergoing no-treatment (control group, $n = 5$).

Intervention – Stent Group

Animals in the stent group underwent a complex endovascular procedure consisting of three parts: recanalization of the thrombotic lesion, thromboaspiration, and stent deployment. One surgeon trained in vascular and endovascular surgery performed all of the operations (VAR).

A 6-Fr guiding contralateral II catheter (Cordis Endovascular, USA) was advanced into the orifice of the left SFA. After per os administration of a loading dose of 150 mg clopidogrel, 125 mg aspirin and 50 units/kg of IV heparin, recanalization of the occlusive thrombotic lesion was performed using a 0.014" hydrophilic intermediate stiffness guide wire (Angioline, Novosibirsk, Russia) (Figure 3*a*). When passed through the occlusion zone, the tip of the guidewire was placed in the popliteal artery.

To evaluate an extension of the occlusive lesion and to prevent distal emboli during stent positioning and deployment, a thromboaspiration procedure was performed. A 6 Fr Eliminate™ aspiration catheter (Terumo, Tokyo, Japan), was passed across the lesion between one and three times, sufficient to permit flow on repeat angiography (Figure 3*b*). A Sinus™ balloon-expandable bare-metal stent (Angioline, Novosibirsk, Russia) was then inserted over the wire and positioned across the lesion. US and angiographic images were used to determine appropriate stent size. The stent was deployed under a nominal pressure of 9 atm (Figure 3*c*). If the diameter of the SFA was slightly larger than previously measured on the US, then a balloon was overinflated to 12–15 atm (rated burst pressure is 18 atm). Following deflation and balloon removal, completion angiography was carried out (Figure 3*d*). At the conclusion of the procedure, catheters, wires, and sheath were removed and manual hemostasis performed for 5–7 minutes.

Intervention – Control Group

For the animals in the control group, no operation was performed or primary anticoagulation administered. Arterial and venous access sheaths were removed 60 minutes after the SFA thrombosis was obtained.

Follow-Up

Following completion of the intervention phase, a post-operative blood sample was drawn and US measurements were taken. The sheep then were extubated and placed into vivarium with free access to food and water.

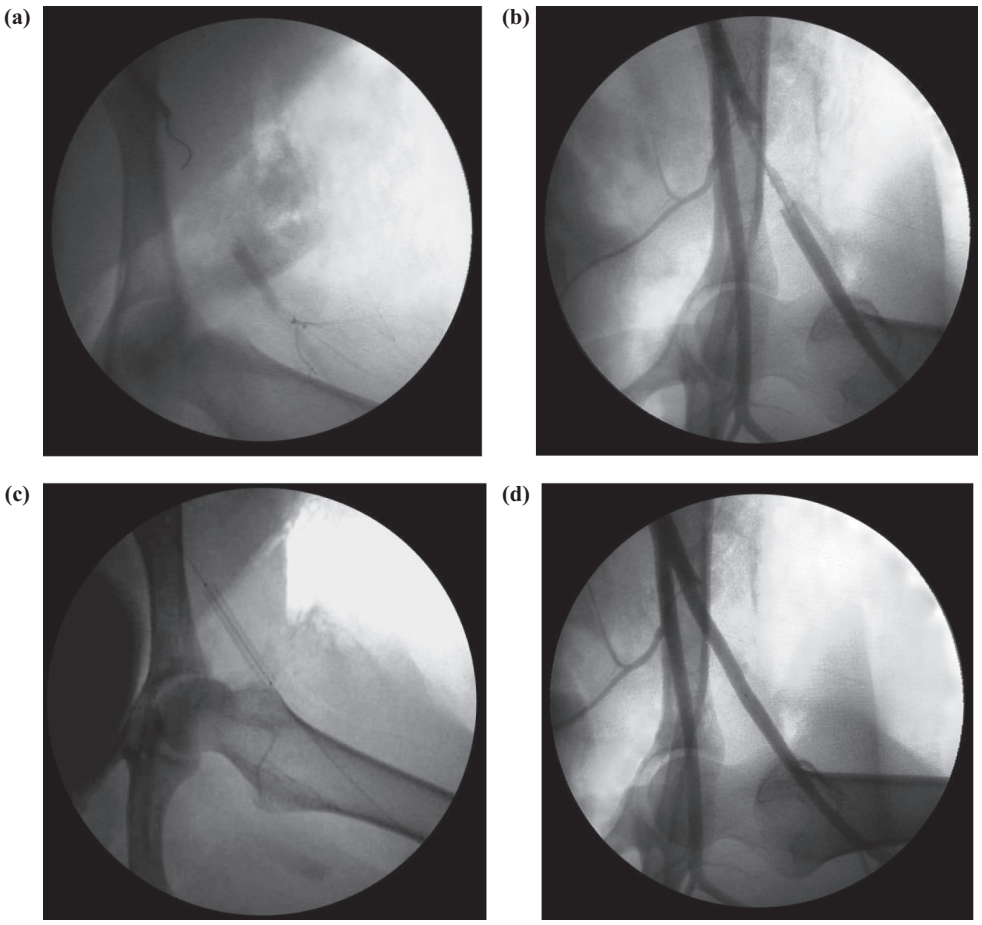

Figure 3 Endovascular sequence for revascularization for the stent group: **(a)** recanalization, **(b)** thromboaspiration, **(c)** stent deployment. **(d)** Completion angiography demonstrates arterial patency.

Postoperatively and daily thereafter, all animals received 1.5 mg/kg of enoxaparin SC and 1.0 g of cefazoline IM. Animals in the stent group also received 75 mg of clopidogrel and 125 mg of daily aspirin. The wound dressing was changed every other day.

Each animal's hind limb function was assessed daily by means of the modified Tarlov hind limb function scale. This is a 5-point ordinal scale from 0 to 4, where 0 is the worst score (unable to sit, paralyzed limb) and 4 the best score (fully ambulatory). US measurements were performed on post-injury day 1, 3 and 7.

On post-injury day 7, the animals in both groups were transported to the operating room and underwent general anesthesia as described earlier. The left carotid artery was instrumented using a 6 Fr sheath. The orifice of each external iliac artery was then selectively cannulated with an MPS catheter, permitting angiography of each extremity. This allowed for an estimation of the patency of the femoral and popliteal arteries. Once the angiography was complete and a final blood sample from the jugular vein was taken, the animal was euthanized by exsanguination under anesthetic.

Study End-Points and Statistical Analysis

The primary end-point of this study was stent patency, which was assessed using a combination of US measurements and angiography. US was used to assess blood systolic velocity (SV), measured in cm/sec and pulsatility index (PI), comparing the left (injured) and right (control) sides at the following time points: pre- and post-injury, and post-operative at day 1, 3 and 7. Each US parameter was valued three times to minimize error. Angiography was performed on day 7 to assess stent patency and the run-off to look for evidence of occluding distal emboli in the branches of the SFA, deep femoral and popliteal artery with its two main branches.

Secondary end-points consisted of laboratory indices of hypocoagulation, reperfusion injury, contrast-induced acute kidney injury (AKI), complications relating to arterial access, functional gait outcomes, and the need for euthanasia due to limb-related problems. Laboratory tests included activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin time (PT), creatinine, urea, and lactate.

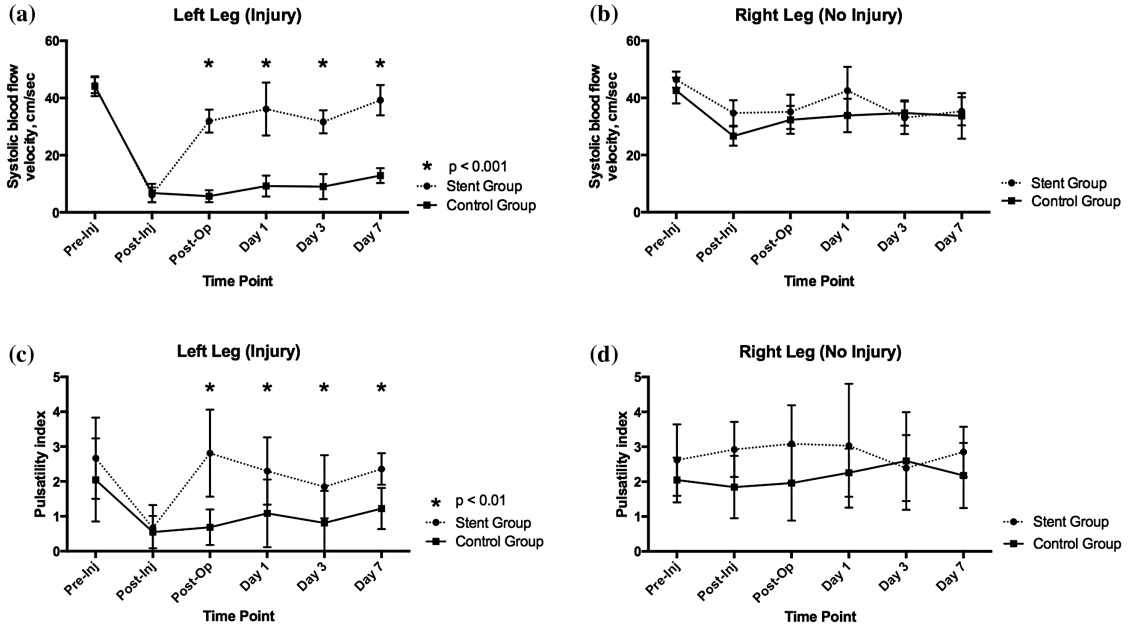

Figure 4 Ultrasonographic measurements of blood flow. Graphs demonstrate a significant increase of **(a)** systolic blood flow velocity (SV) and **(c)** pulsatility index (PI) in the left (injured) leg and no changes in **(b)** SV and **(d)** PI in the right (control) leg in post-operative period and during the 7-day observation period.

Data were analyzed using GraphPad Prism v6.0 (Graphpad Software Inc., La Jolla, CA, USA). Variables were evaluated for normal distribution, and nonparametric data were reported as medians with interquartile ranges (IQRs). Between-group and within-group comparisons were performed using a two-tailed Mann–Whitney *U* test. Data for two groups with repeated measures were assessed with two-way analysis of variance (ANOVA). A *post hoc* Bonferroni correction was applied for multiple comparisons. Chi-square test was used to compare ordinal data. Fisher's exact test was used to compare SFA patency rate between groups. Results were considered significant when $P \leq 0.01$.

RESULTS

Baseline Characteristics, Arterial Injury, and Intervention

A total of ten sheep underwent induction of a traumatic SFA thrombosis and were then randomized into either the stent ($n = 5$) or control ($n = 5$) groups. There were no significant differences observed between the groups when comparing baseline characteristics, laboratory tests or hemodynamic parameters (Tables 1 and 2).

An occluding thrombosis was successfully created in all animals, as observed on angiography, taking on average 60 mins to achieve (Table 1). This was confirmed by US flow indices, which fell when comparing the pre- to post-injury values in the left limb (Figure 4). The fall in SV was similar for both the control (43 (36–56) to 6 (0–16); $P < 0.001$) and stent groups (45 (32–53) to 8 (0–12); $P < 0.001$). There was no significant change in US indices measured in the uninjured limb for either group.

Recanalization of the occlusive thrombi was the most time-consuming part of the whole procedure taking 80 minutes on average (Table 1). It was likely due to significant intima-media injury resulting from an excessive force applied to a vessel wall during the creation of the injury. After passing the occlusion, all animals allocated to the stent group underwent successful deployment of a balloon-expandable bare-metal stent, across the zone of arterial injury. No distal emboli were observed on angiography at the time of stent deployment.

Primary Outcome: Stent Patency

Stent deployment saw the restoration of inline flow through the SFA on angiography. This was accompanied by a significant rise in SI and PI measurements when comparing the stent group against the control group (Figure 4). These changes were sustained through to day 7, when angiography confirmed SFA patency in all (5/5) stented animals, with persisting occlusions in the controls (Table 1; $P = 0.008$). There was no evidence of distal emboli in the run-off arteries on angiography at day 7. There were no significant differences in US measurements recorded between the stent and control groups in the uninjured limb.

Table 1 A comparison of baseline, operative and follow-up characteristics between groups.

Parameter	*Stent Group*	*Control Group*	*P*
n	*5*	*5*	
Female	5 (100%)	5 (100%)	
Weight, kg	39.0 (36.5–41.0)	38.0 (36.5–41.0)	0.976
Physiology			
Heart rate, beats/min	71 (60–82)	88 (62–105)	0.341
Systemic SBP, mmHg	110 (105–121)	107 (103–128)	0.857
Thrombosis			
Time to creation of injury, min	60 (60–105)	60 (60–150)	0.841
Operative			
Anesthesia time, min	300 (225–330)	210 (180–270)	0.143
Operative time, min	80 (63–120)	–	–
Intraoperative fluids, mL	950 (740–1,125)	800 (650–960)	0.548
Intraoperative heparin, U	4,000 (3,500–4,500)	500 (400–550)	0.008
Volume of contrast medium, mL	100 (100–113)	40 (40–55)	0.008
Tarlov gait score			
Day 1	2 (2–2)	2 (2–3)	0.970
Day 3	3 (3–4)	3 (3–4)	0.990
Day 7	4 (4–4)	4 (4–4)	1.000
Arterial data			
Diameter of SFA, mm	4.0 (3.8–4.0)	3.5 (3.5–4.2)	0.524
EOS Patency (%)	5/5 (100)	0/5 (0)	0.008

Values are median (IQR). Mann–Whitney U Test is used to compare continuous data, chi-square test and the Fisher's exact test is used to compare Tarlov gate score and the patency of the targeted SFA, respectively.
EOS, end-of-study; SBP, systolic blood pressure; SFA, superficial femoral artery.

Table 2 A comparison of end-of-study characteristics between groups.

Parameter	*Stent Group*			*Control Group*			*BL*	*EOS*
	BL	*EOS*	*BL vs. EOS*	*BL*	*EOS*	*BL vs. EOS*	*SG vs. CG*	
			*P**			*P**	*P**	*P**
Hb, g/dL	10.3 (9.0–11.1)	9.3 (9.3–9.8)	0.206	10.1 (8.8–11.0)	9.9 (8.1–10.7)	0.460	0.794	0.881
RBC, $\times 10^{12}$/L	9.9 (3.3–11.3)	9.1 (3.4–9.6)	0.548	9.4 (8.4–12.3)	9.2 (7.4–12.0)	0.841	0.691	0.421
WBC, $\times 10^{9}$/L	44.1 (22.6–56.4)	35.0 (9.2–44.7)	0.310	42.8 (12.4–52.5)	47.2 (27.8–49.5)	0.841	0.841	0.095
Platelets, $\times 10^{9}$/L	180 (115–310)	470 (457–490)	0.100	236 (211–506)	364 (261–629)	0.746	0.250	0.250
APTT, s	47.3 (39.0–64.8)	36.1 (33.4–49.8)	0.421	45.4 (30.4–48.6)	35.2 (26.3–40.1)	0.222	0.421	0.310
PT, s	37.3 (34.9–39.0)	36.0 (24.0–42.0)	0.886	34.3 (31.0–40.0)	41.0 (31.3–53.4)	0.310	0.413	0.286
INR	2.4 (2.2–2.5)	2.3 (1.4–2.8)	0.886	2.2 (1.9–2.6)	2.7 (2.0–3.7)	0.310	0.413	0.286
Lactate, mmol/L	2.2 (1.5–2.9)	3.9 (2.2–7.2)	0.151	2.1 (1.4–3.6)	2.1 (1.7–2.9)	0.999	0.999	0.151
Urea, mmol/L	6.4 (5.7–7.2)	9.9 (7.9–12.7)	0.016	11.1 (7.4–13.0)	11.8 (6.4–12.9)	0.905	0.032	0.999
Crea, μmol/L	34.3 (25.5–38.1)	35.2 (6.2–67.5)	0.999	51.1 (35.2–82.2)	64.6 (36.9–83.5)	0.999	0.143	0.310

*Values are median (IQR). *Mann–Whitney U Test.*
APTT, activated partial thromboplastin time; BL, baseline; CG, control group; Crea, creatinine; EOS, end-of-study; Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cells; SG, Stent group; WBC, white blood cells.

Secondary Outcomes: Laboratory Indices, Limb Function, and Morbidity

Table 2 reports the laboratory indices recorded at baseline (BL) and end-of-study (EOS). The only parameter to trend toward a significant difference was the urea value in the stent group demonstrating a tendency to AKI due to much more contrast agent administered to animals of this group (Table 1). This saw a rise from 6.4 (5.7–7.2) at BL to 9.9 (7.9–12.7) at EOS, although this did not achieve statistical significance ($P = 0.016$).

The experimental protocol did not result in a significant reduction in limb function. The lowest Tarlov gait score took place on post-injury day 1, while all animals demonstrated an improvement in their scores over time (Table 1). By day 4, the majority of animals has achieved a Tarlov score of 4, with all animals fully ambulatory by day 7. There was no significant difference in Tarlov gate

score between the groups at any time point including EOS (Table 1).

All animals were followed up to day 7, with none requiring euthanasia. No cases of death or limb necrosis were observed in either group. One animal in the stent group had sustained a puncture site hematoma (pseudoaneurysm excluded by US) which had completely resolved by post-operative day 3.

DISCUSSION

The current study is the first to report the performance of bare-metal stents in an ovine model of traumatic arterial occlusion. An endovascular procedure consisting of recanalization, thromboaspiration, and stenting was demonstrated to be effective in restoring and maintaining arterial patency for the 7-day duration of the study. End-of-study angiography did not identify any evidence of distal emboli and no animal requiring euthanasia for a limb-related complication.

This work builds on our group's research into the management of traumatic arterial occlusion. We have previously described the injury model employed in this study, which demonstrates the ease with which a reproducible occlusive lesion can be produced, with minimal animal morbidity [9]. Within that study, we also successfully demonstrated the compatibility of human endovascular maneuvers within the ovine arterial tree. The current study expands upon this work, by formally assessing the performance of a bare-metal stent compared to a control group, using this injury model.

Few investigators have sought to examine the role of stents and stent-grafts in large animal models of arterial injury. Most models have been developed to investigate mechanisms of vascular trauma [10,11], methods of diagnosis [12] and the efficacy of open surgical treatment [13–15]. The majority of the published literature in regard to stents and stent-grafts relate to long-term biocompatibility testing of new devices in normal arteries [16–18].

In a recent paper, Tang and co-workers proposed the deployment of a covered stent through an open incision in order to permit revascularization [19]. The authors created a 2-cm defect of the ovine SFA and then deployed a covered stent inside through a distal arteriotomy. Aspirin 325 mg was administered and US revealed 5/8 stents patent at 2 months postoperatively. Overall, their view was that this technique held promise for surgeons unfamiliar with vascular anastomoses, but required further study.

This is in contrast to the clinical evidence published in regard to endovascular intervention in trauma. Several large retrospective registry studies have seen a year-on-year increase in the reporting of endovascular technique in trauma [3,5,7]. However, the introduction of these techniques has been very informal and relate to the *ad hoc* extension of techniques employed in vascular disease to trauma.

The most detailed clinical data published to date is from the prospective PROOVIT registry [4]. Occlusive arterial injuries occurred in 17.7% of patients sustaining a vascular injury, although only 7.4% were managed by endovascular means. The most common arteries treated by endovascular means were the aortic and iliac segments.

The current study builds on this evolving evidence base by using a standardized model to test a bare-metal stent, in "ideal" trauma circumstances, ie: where anticoagulation was permitted. The choice of stent in this study is unusual, in that most clinicians would elect to use a fabric-covered stent-graft, usually incorporating a self-expanding alloy such as nitinol. While a stent-graft may appear an intuitive choice, for a purely occlusive lesion, there is no strong evidence supporting either type of conduit.

A balloon-expandable bare-metal stent has the advantage of precise deployment control, coupled with the option to increase the diameter in the event of undersizing while being relatively inexpensive compared to self-expanding stent-grafts. In theory, thrombus can protrude through the metal to initiate an in-stent thrombosis or distal embolism. No instances of either were observed in the current study. A drawback of bare-metal stents is their rigidity, thus a relatively akinetic segment of artery was selected, as deployment across joints and mobile regions is contra-indicated. It is especially important for the young and healthy trauma population, where long-term patency has not been well investigated and open vascular repair likely remains the gold standard.

There are several limitations to discuss. The current study is small, only consisting of two groups of five animals and thus should only be characterized as a pilot study. The "control" group consisted of no intervention which does not necessarily reflect current practice, where an interposition graft or similar could have been fashioned.

Animals of the stent group were administered dual antiplatelet therapy according to a current protocol for peripheral arterial interventions [20,21]. Relatively high daily dosages of both clopidogrel and aspirin were given as recommended in some ovine models [19,22–24]. Connel et al. found that the sheep, weighing even less than our animals, 17–35 kg, had a modest antiplatelet response (platelets inhibition by 25–36%) to 75 mg of daily clopidogrel [22]. The dose of aspirin that the sheep receive varies between studies, but doses of 81 or 325 mg of daily aspirin prevail [19,23–25]. As long as aspirin has shown to be ineffective in the inhibition of platelet aggregation in sheep [26], we chose a mid-dose taking into account that no clear recommendation and evidence exists.

Furthermore, a follow-up period of 7 days can only really assess early in-stent thrombosis and gives no indication of the risk in later occlusion. The long-term aim is to extend this model to a much longer follow-up (e.g., months) in future study protocols.

Finally, and most importantly, trauma rarely happens in isolation, which has significant local and systemic effects. Hemorrhage and tissue injury can result in both

hypo- and hypercoagulable states, a source of considerable concern when implanting an endo-prosthesis. In the current study, the isolated injury was anti-coagulated with both heparin and dual antiplatelet agents – circumstances rarely permissible in trauma care, especially in the setting of a concomitant head injury.

Despite these limitations, the current study adds to the evidence base surrounding this emerging intervention, by demonstrating the feasibility of bare-metal stenting in occlusive vascular trauma. The methods and models used in this study now need extending to more complex lesions, including significant blood loss, different types of graft, with and without anticoagulation and/or platelet inhibitors and for longer follow-up periods.

CONCLUSIONS

The present study demonstrates that bare-metal stent implantation appears to perform well in the setting of a standardized ovine model with a short follow-up period. Minimal morbidity was incurred and the ovine arterial tree appears well suited to endovascular research. However, this conduit requires comparison with other methods of revascularization and a longer term of study in order to better appreciate its role in traumatic vascular occlusion.

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