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Evaluation of an Absorbable Cyanoacrylate Adhesive as a Suture Line Sealant[1]

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Background. **Previous formulations of cyanoacrylate, though very effective, proved to have too high a tissue reactivity to be used internally. A novel cyanoacrylate compound with less tissue reactivity was recently developed. The objective of this study was to assess this novel cyanoacrylate compound for the use as vascular suture line sealant.**

Materials and methods. **Twelve adult female sheep received a 6 mm PTFE interposition graft in each iliac artery, for a total of 24 grafts. Using oxidized cellulose (Surgicel) as a control, two formulations of a new cyanoacrylate compound (named "compound A" and "compound B") were assessed during this trial. Hemostatic efficiency was measured at the time of operation by the assessment of bleeding time and amount of blood loss. Long-term graft patency was assessed angiographically at 4, 6, and 18 months. Tissue reaction at 2 weeks, 1, 6, and 18 months was assessed grossly by vascular surgeons and microscopically by a blinded pathologist.**

Results. **Average time to hemostasis was 37.6, 50.6, and 219 s in group A, group B, and oxidized cellulose control groups, respectively ($P \leq 0.001$ for both compounds *versus* control). There were no significant differences between groups with regards to graft patency. Histopathology analysis demonstrated mild to moderate tissue reaction at 2 weeks and 1 month in the cyanoacrylate groups compared with controls at 1 month (ANOVA $P = 0.004$). Mild tissue reaction was seen at 6 months and 18 months, with no significant differences between groups (ANOVA $P = 0.08$, 0.62, respectively).**

Conclusions. **The novel cyanoacrylate compound examined in this study is a highly effective suture line sealant with only mild tissue reactivity and no significant effects on graft patency when studied over an 18 month period.**

Key Words: **vascular surgery; anastomosis; PTFE; cyanoacrylate; biomedical engineering; tissue adhesives; glue; oxidized cellulose; hemostasis; vascular research.**

INTRODUCTION

Bleeding at the anastomotic suture-line is a significant clinical problem that can lead to increases in operative time and patient morbidity [1]. While this is a problem with all types of anastomoses, it is particularly so with PTFE. Moreover, with the use of antiplatelet agents such as the Plavix product becoming more widespread, issues with suture line bleeding have become more prevalent. Although there are a number of tissue adhesives currently available for use as a suture line sealant, most surgeons will only turn to the use of these compounds when conventional means of hemostasis fail.

Since its discovery in the 1940s, cyanoacrylate has been evaluated as a potential tissue adhesive. Earlier forms of cyanoacrylate caused extensive tissue reaction, and thus could not be used as a tissue adhesive [2]. Over time more stable forms of the compound were developed, and now Dermabond Topical Skin Adhesive (Closure Medical Corp., Raleigh, NC) (formulated 2-octylcyanoacrylate) is currently FDA approved for

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topical use to hold closed easily approximated skin lacerations [3]. Because of the previous concerns about tissue reaction, as well as some concerns over the potential carcinogenicity of the earlier compounds, cyanoacrylate adhesives have not yet been approved for internal use. These earlier forms of cyanoacrylate were non-absorbable, and moreover, were purported to be carcinogenic [4]. Despite these early claims, others have subsequently failed to demonstrate that cyanoacrylate compounds possess carcinogenic properties [5].

Closure Medical Corporation (Raleigh, NC) has recently developed a new cyanoacrylate composition. In preliminary tests, this compound had mild tissue reactivity, as well as a capacity to be absorbed. Formaldehyde, which in high quantities can be toxic to tissues, is a product of the degradation process of cyanoacrylate compounds. Early versions of CAs had uncontrolled degradation, and the concentration of degradation products was high, leading to tissue reaction and inflammation. This new formulation degrades in a relatively controlled manner, and thus the concentration of the degradation products is very low on a per day basis. This stability has been achieved by the addition of organic chemical groups to the backbone of the cyanoacrylate compound.

Given these preliminary tests, we hypothesized this compound potentially be used internally as a vascular suture line sealant with no added toxicity to the surrounding tissues.

METHODS

Animal Care and Use

All experiments were conducted under a research protocol approved by the University of Virginia Institutional Animal Care and Use Committee. All animals received humane care in compliance with the "Guide for Care and Use of Laboratory Animals" [6].

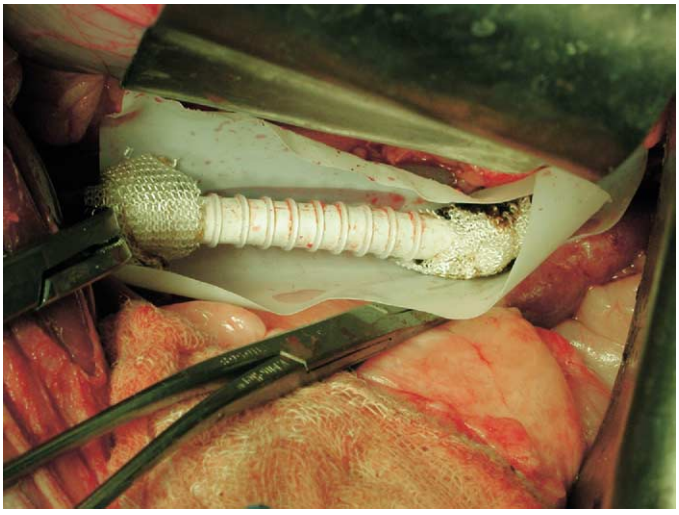

FIG. 1. This figure demonstrates the way in which the oxidized cellulose was applied before the clamps were removed in the control group. (Color version of figure is available online.)

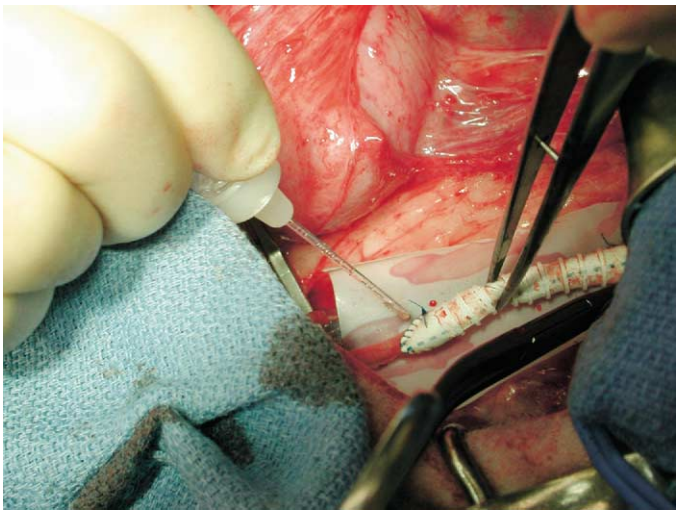

FIG. 2. Cyanoacrylate compound A or B was applied to the suture line sparingly before clamps were removed. After the compound was applied the surgeon would wait approximately 1 min before clamps were removed. (Color version of figure is available online.)

Experimental Protocol

Twelve adult female sheep received a 6 mm PTFE interposition graft in each iliac artery, for a total of 24 grafts. Each graft was randomized to receive oxidized cellulose (Surgicel hemostat) as a control, or cyanoacrylate adhesive. Given the fact that this compound was still in experimental stages, Closure Medical Corporation supplied two similar, but not identical formulations. These formulations were identified as compound A and compound B. Thus, eight grafts received oxidized cellulose (Control) at each anastomosis site (proximal and distal), eight received cyanoacrylate compound A (group A), and eight received cyanoacrylate compound B (group B). Intra-operative bleeding time and total blood loss were assessed. Three animals were euthanized for gross and microscopic histopathologic evaluation at 2 weeks, 1 month, 6 months, and 18 months, respectively. Angiography was performed at 4, 6, and 18 months.

Operation

After midline incision, the abdominal contents were exposed. The iliac arteries were then exposed bilaterally using sharp dissection and electrocautery. Before clamping the first iliac artery, the sheep were anticoagulated with an intravenous injection of heparin (200 units/kg). This dose maintained an activated clotting time (ACT) of over 300 s throughout the case. Blood samples were obtained initially and at 30 min intervals to document that the sheep remained anticoagulated. If the ACT dropped below 300 a supplemental dose of heparin was given. Upon completion of the second procedure (after an analysis of hemostasis), heparin was reversed with Protamine (1 mg/kg i.v.).

After heparinization, the exposed iliac artery was occluded between atraumatic vascular clamps and a 3 cm segment of artery was excised. Using 6 mm PTFE, a 6 cm interposition graft with spatulated ends was then anastomosed proximally and distally with running 5-0 polypropylene suture. Upon completion of the anastomoses the surgeon was then given either oxidized cellulose (Fig. 1), cyanoacrylate compound A or cyanoacrylate compound B for application at