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Glue-Enhanced Excimer Laser-Assisted Nonocclusive Anastomosis: A Laboratory Investigation

Alex Alfieri[a, b] Michael Reinert[b]

[a]Department of Neurosurgery, Martin Luther University Halle-Wittenberg, Halle/Saale, Germany;
[b]Department of Neurosurgery, University Hospital Inselspital, Bern, Switzerland

Key Words
Excimer laser anastomosis · Cerebral bypass · Rabbit bypass · Bypass, experimental · Glue

Abstract
Background/Aims: The excimer laser-assisted nonocclusive anastomosis (ELANA) technique has been developed as a clinical effective technique to perform intracranial high-flow bypass without temporary occlusion of cerebral vessels in otherwise untreatable or high-risk cerebrovascular diseases. We experimentally tested the application of a nonabsorbable cyanoacrylate-based sealant with the ELANA technique. ***Methods:*** Three technical in vitro variations of the ELANA anastomosis technique using Omnex© glue and expanded polytetrafluoroethylene tube were compared with conventional sutured ELANA bypasses, resulting in 36 bypasses and 72 anastomoses. After that, the best resulting type was tested in 10 rabbits. ***Results:*** The ELANA bypass using Omnex and the expanded polytetrafluoroethylene tube technique offers better results in vitro in the retrieval of the arterial wall flap after arteriotomy, is faster, and the tensile strength of the bypasses performed with Omnex is comparable with those performed with conventional sutures. However, in 2 cases, we observed thrombosis of the vessel and considerable stiffness. ***Conclusions:*** The combining of the ELANA technique with 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate experimentally provides some advantages over the conventional ELANA technique. Further experimental studies should be performed in order to improve the safety and applicability of this technique.

Introduction

The excimer laser-assisted nonocclusive anastomosis (ELANA) technique has made it possible to use a clinically valuable technique to perform intracranial high-flow bypasses without transitory occlusion of cerebral vessels in otherwise untreatable diseases, such as giant aneurysms, invasive skull base tumors and cerebrovascular deficiency [1–8]. The major advantage of this technique is the avoidance of a significant period of temporary occlusion of the recipient vessel and the decrease in not necessarily technical difficulties [9]. A highly specialized team was trained comprising a microsurgeon, a scrub nurse, a laser technician and possibly a microvascular training laboratory as it restricts the established ELANA technique. Furthermore, there is an exercise-dependent success rate of the ELANA anastomosis, which is the result of the flap retrieval rate.

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Alex Alfieri, MD
Department of Neurosurgery, Martin Luther University Halle-Wittenberg
Ernst-Grube-Strasse 40, DE–06120 Halle/Saale (Germany)
Tel. +49 345 557 1407, Fax +49 345 557 1412
E-Mail alex.alfieri@medizin.uni-halle.de

The further development of the ELANA technique with a view to reducing the number of microsutures, increasing the flap retrieval rate, and minimizing the time of the procedure may be helpful in the advance of a faster and secure minimally invasive bypass technique as shown recently [8, 10, 11].

Therefore, we experimentally assessed the effectiveness of an enhancement of the ELANA technique using a nonabsorbable cyanoacrylate-based sealant.

Materials and Methods

The present study analyzes first in an in vitro model the ELANA bypass technique using different concepts of the application of the sealant and thereafter experiments with in vivo effectiveness in the rabbit. All the experiments were conducted at the Neurovascular Laboratory of the University Hospital Inselspital of Bern (Switzerland). The study was approved by the Ethical Commission of the Canton Bern, Switzerland (No. 95/06). All experiments were performed in random order by type so as to remove any practice effect.

In vitro Study

Fresh rabbit abdominal aortas (Soltermann, Thörigen, Switzerland) were fixed to the ELANA training model and the perforators and branching arteries were sealed with 8-0 sutures (Prolene; Ethicon, Johnson & Johnson, Spreitenbach, Switzerland) to prevent leakage, thereby simulating an adequate intravascular blood tension. For further details of the model, we refer to a previous description [16].

In order to optimize the surgical advancements obtained through the glue, 4 technical variations (types A, B, C and D) of the conventional ELANA anastomosis technique were experimentally considered. Consequently, we use the procedure with the best results.

Type A. Fixation of the 2.6-mm platinum ring (ELANA BV, Utrecht, The Netherlands) was performed with eight stitches of 8-0 polypropylene monofilament sutures. The donor artery was connected to the receiving artery using glue and four stitches.

Type B. In the type B bypass, the platinum ring was inserted on the outside of the donor artery, at 5 mm from the tip, and fixed with four stitches. After this, two incisions were made into the graft wall from the end of the graft in the axial direction towards the ring, ending at a distance of between 3 and 5 mm (1–2 times the graft wall thickness). The graft with the ring was afterwards put onto the side of the artery at the desired position. It was then fixed there with two sutures, the coattails extending away from the graft lumen on the outside of the artery. The sealant was spread into a thin and uniform film in the inert part of the coattails and gently tailored on the surface of the receiving artery.

Type C. In the third model (type C) the same procedure as with type B was used, but employing as donor vessel an expanded polytetrafluoroethylene tube (ePTFE; L. Gore and Associates, Newark, N.J., USA), as previously described [1].

Type D. In the type D (control group), with the microsurgical conventional technique, a fresh rabbit aorta was used as the donor artery. It represents the standard ELANA bypass. Each type of bypass was performed 9 times, resulting in 36 bypasses and 72 anastomoses.

Sealant Glue Specifications

The surgical sealant selected for this study was Omnex© (Ethicon, Johnson & Johnson), a synthetic, commercially available absorbable adhesive tissue consisting of a blend of two monomers, 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate. This glue sealant was tested earlier in cardiovascular surgery [12–14]. The application in the experimental models was performed according to the specifications of the manufacturer using the sterile device provided. The liquid formulation is contained in a crushable glass ampoule, which is housed inside a molded unit. The formulation is passed through a porous disc containing an initiator, mixed in a chamber and delivered through a conduit. The glue was applied to the anastomosis with supplementary adjunct on the applicator's cannula of a smaller tube obtained by cutting a 26-gauge intravenous needle (BD Neoflon; Becton Dickinson Infusion Therapy AB, Helsinborg, Sweden) in order to improve the handling under the microscope and to reduce the risk of intravasal contamination.

Laser Arteriotomy Specifications

After performing the end-to-side sealant-enhanced anastomosis, the bypass was accomplished using the excimer laser catheter (X80; Spectranetics International BV, Leusden, The Netherlands) into the bypass graft using the ELANA protocol as previously described [15, 16]. High vacuum suction with a compressor for 120 s was applied in all cases. The excimer laser was constantly activated for 5 s with output energy of 30 mJ/m^2 and a pulse frequency of 40 Hz. The pulse length was of 100 ns at a light frequency of 308 nm.

Anastomosis Quality Assessment

The bypasses were then tested with pressure burst gauging and finally the tensile strength was measured with a fixed force gauge tensile testing machine BFG50 (Mecmesin Ltd., Slinfold, UK) and a moving table to pull the two soldered tissue samples apart using fixed surgical clamps. With a pressure of 200 mm Hg without leakage the pressure burst was considered passed. The force necessary to tear the graft extremities perpendicularly was calculated in newtons (N = kg/s^2).

In vivo Experiments

All rabbits were cared for in accordance with the Principles of Laboratory Animal Care (National Society for Medical Research) and the Guide for the Care and Use of Laboratory Animals (National Institutes of Health). The study was approved by the Ethical Commission of the Canton Bern (No. 95/06). All surgical procedures were performed under optimal sterile conditions.

According to the results obtained in the in vitro experiments, we selected the best design for the animal experiments.

Animal Preparation. Ten New Zealand White rabbits (Magnin, Fribourg, Switzerland) weighing 3–3.5 kg were used for this study. After arrival at our laboratory, the animals were acclimated for at least 7 days before undergoing any surgical procedure. They were provided with approximately 180 g of rabbit chow daily and water ad libitum. Food was withdrawn from surgical candidates in the morning of the operation. On the day of surgery, the animals were

weighed and given an intramuscular injection of 5 mg/kg of enrofloxacin (Baytril) as a preoperative antibiotic prophylaxis.

Premedication and Anesthesia. Anesthesia was induced with a combination of ketamine (30 mg/kg) and xylazine (6 mg/kg) injected intramuscularly. The marginal vein of the ear was cannulated with a 24-gauge intravenous catheter, flushed, and closed with an injection cap. The animal was secured on the operating table in dorsal recumbence, and the surgical sites were cleaned and disinfected with octenidine hydrochloride/phenoxyethanol (Octenisept; Schülke Mayr AG, Zürich, Switzerland). Body temperature was maintained between 36 and 37°C with a heating pad placed underneath. The animal was then orotracheally intubated and ventilated mechanically. The anesthesia was then continued with fluorane. The surgical anesthesia was produced and maintained by intermittent intravenous infusions of 0.2–0.3 ml of 2% methohexital sodium (Brevital) solution in saline. An infusion line was attached to the catheter in the marginal vein by means of a 25-gauge butterfly needle. Each rabbit was hydrated with 20 ml/kg lactated Ringer's solution supplemented by intravenous drip throughout the operation.

Laparotomy and Aorta Bypass. The abdomen was shaved and disinfected. After covering with disinfectant a midline abdominal incision was performed, and bleeding was controlled by electrocautery. The intestines were displaced to the right side and covered with gauze moistened with warm saline solution and surrounded by sterile aluminum foil. Thirty millimeters of the infrarenal abdominal aorta were freed from the surrounding tissues and separated from the inferior vena cava. The outer diameter of the aorta at the bypass site was measured with a micrometer. Aseptic conditions were maintained during the surgical procedures, which were performed by using a Zeiss OPMI 1 operating microscope. The aortic branches in this segment were ligated definitively with 4-O silk sutures or miniclips. Heparin (200 U/kg) was administered intravenously shortly before the laser perforation. The anastomosis was then performed in an end-to-side fashion according to the type 2 of the in vitro experiment. An ePTFE tube was prepared for end-to-side anastomosis. The placing of two interrupted, equally spaced, 8-O polypropylene monofilament (Prolene; Ethicon, Johnson & Johnson) sutures connected securely and precisely the ends of the coattails. The target area was dry and free from biological fluids and the glue was carefully applied between coattails and recipient vessel, with rapid achievement of an anastomosis. After 2 min the polymerization was completed and the sterilized excimer laser catheter was introduced. The excimer laser catheter (X80; Spectranetics International BV) was introduced into the bypass graft, and pushed up until the tip touched the wall of the recipient artery inside the platinum ring. For 120 s high vacuum suction was applied to achieve a firm fixation of the tip of the laser catheter. The excimer laser was then activated for 5 s with 30 mJ/m^2 and 40 Hz. The tip penetrated the wall and entered the lumen of the recipient artery up to the platinum ring. The catheter was withdrawn together with the pouched-out portion of the recipient artery. The nonocclusive anastomosis was finally completed, and the bypass graft was transitorily occluded with a temporary aneurysm clip. The same procedure was then repeated at the other vascular end. A conventional end-to-end microsuture between the two grafted vessels was performed, creating the bypass. Additionally, stitches were placed where needed. Once hemostasis was achieved, the intestines were placed in their normal position, and the abdominal wall was closed with an absorbable suture (4 Vicryl) in a running fashion. The skin was at that time closed subcuticularly using a 3-O Vicryl suture, and the wound was treated with octenidine hydrochloride/phenoxyethanol (Octenisept). The animal was then placed in a cage with a warm hot water bottle and extubated. The animals were allowed food and water immediately postoperatively. They received analgesic treatment (buprenorphine injection 0.1 ml/kg s.c.) twice daily for 3 days after the operation and as needed thereafter. The animals were checked daily for signs of intra-abdominal hemorrhage.

Bypass Assessment. The animals underwent another surgical procedure within 4 weeks from the first procedure, at various times from the operation as necessary for the short-term follow-up. They were anesthetized with an intramuscular injection of ketamine (35 mg/kg) and xylazine (7 mg/kg). Angiography was then performed for assessment of the bypass patency (Leuag AG, Stans, Switzerland; matrix 1,024 × 1,024 biplanar) using contrast agent (Iopamiro; Bracco Swiss S.A., Mendrisio, Switzerland). At the predetermined times the animals underwent a reoperation. The surgical site was examined for adhesions, fibrosis, postoperative bleeding, hematoma, and residual fibrin clot. The vessels were pressure fixated with formaldehyde through the subclavian artery and a cut in the femoral artery. The abdominal aorta including the bypass was extracted and fixed in formaldehyde and later embedded into methylacrylate resin to obtain the tissue slices with the platinum ring. After pretreatment with paragon solution the slices were stained using hematoxylin and eosin. The fixed vessel was sectioned longitudinally and stained with Movat's pentachrome stain. Subsequent to this assessment, the animals were administered a lethal dose of pentobarbital (100 mg/kg).

Statistical Analysis

Tensile strength data are presented as means ± SEM. The statistical significance was determined at $p < 0.05$. The data were analyzed using the commercial software SPSS version17.0.0 (SPSS Inc., Chicago, Ill., USA). For multiple groups an ANOVA analysis was performed.

Results

In vitro Findings

The measured tensile strength was 1,524.4 mN (±574), 2,528.9 mN (±510) and 2,492 mN (±287), respectively, for the anastomoses types A, B and C. The sutured type D (control) reached a strong peak of 2,611 mN (±376) (fig. 1). We found statistically significant differences between the anastomoses types B and C, and type A ($p < 0.004$). However, type C had the most convenient standard deviation of all groups. No significant statistical difference related to the tensile strength was found between group B and C and the control group ($p = 0.71$). The perforation with the excimer laser was achieved in all cases. The disc of the arterial wall (flap rate) was successfully punched out in 94.4% of the glue-assisted groups, whereas the flap retrieval rate in the sutured group was 66.6% (fig. 2). The burst pressure test was passed in all but one case.

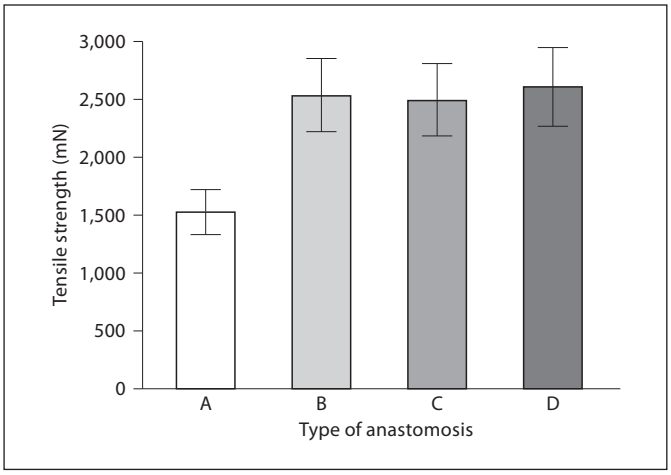


Fig. 1. The mean tensile strength was measured using the force gauge testing machine BFG50 (Mecmesin). Groups B–D had significantly better results with the t test compared to group A ($p < 0.001$). No statistical difference was found between groups B–D ($p = 0.84$). Group C showed the most favorable standard deviation.

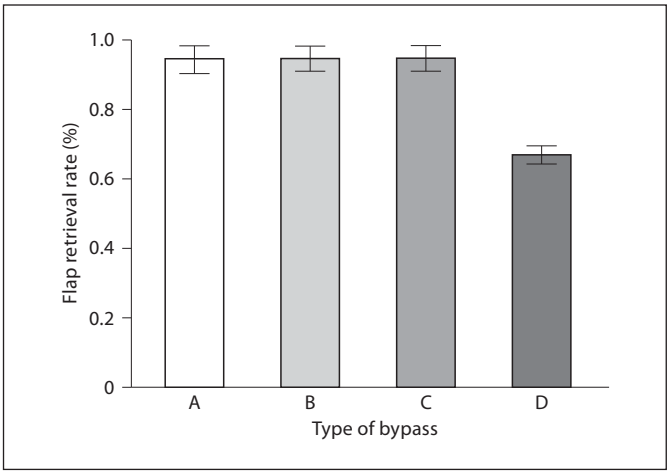


Fig. 2. The column graph shows the homogeneously high percentage (94.4%) of flap retrieval after arteriotomy using the excimer laser nonocclusive technique. All the groups with Omnex were statistically significant ($p < 0.0002$) with respect to the control group (type D).

The mean time to perform the in vitro bypass was 69.5 min (SD 18.8), 71.55 min (SD 20.5), 72.11 min (SD 16.3) and 111.55 min (SD 14.3), respectively, for types A, B, C and D. The same surgeon performed the experimental procedures. There was a statistical significance between the glued types A, B and C, with respect to the conventional suturing technique ($p < 0.002$), with a mean reduction of 40.1 min (fig. 3).

In vivo Findings

As a result of the in vitro results, the end-to-side type C model was used for the animal series. The outer diameters of the aorta at the bypass site were 2.2 ± 0.4 mm.

One rabbit died from exsanguination after the excimer laser perforation, due to imprecise hardening of the glue over the laser catheter and bleeding after the laser application. The remaining animals achieved immediate and complete hemostasis. The ePTFE was acutely occluded by thrombosis within 48 h in 2 cases. In the remaining cases the graft was functioning and patent. The flap was retrieved in all cases. No vessels were damaged macroscopically by the glue application. We noted that the Omnex glue is rather stiff and hardens rapidly, leading to some problems with in vivo use.

Gross Pathological Findings

The surviving animals were euthanized, according to the protocol, within 4 weeks at different times after the operation. At the reexploration, no gross evidence of hematoma formation or recurrent bleeding was observed. The bypass segment was covered with thin fibrovascular uncolored tissue. The tissues were hardly detachable from the vessel, allowing observation of the growth of the

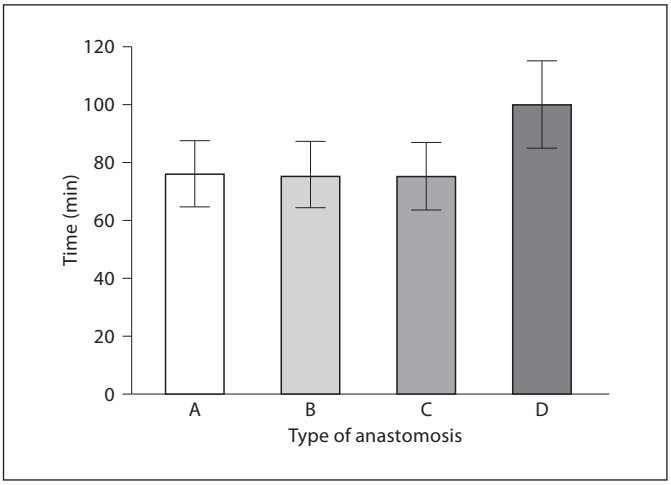
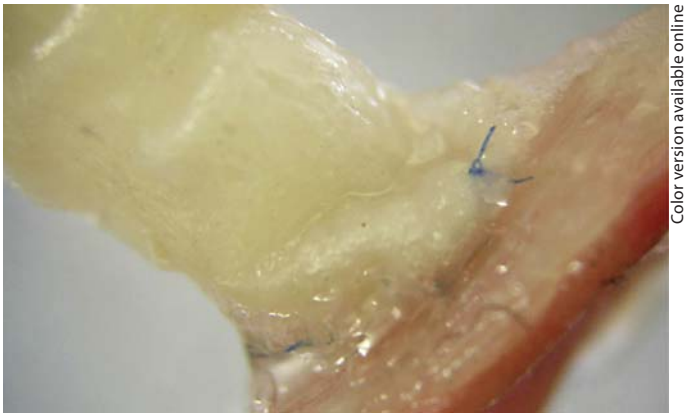


Fig. 3. The column graph shows the mean time necessary to perform the entire procedure. The conventional suturing technique using the ELANA arteriotomy (type A) was statistically longer compared to the glue-assisted type ($p < 0.0002$), with a mean reduction time of 40.1 min. To reduce the bias due to the learning curve the types of procedure were randomly determined.



Color version available online

Fig. 4. Bypass after removal from the animal. The bypass site is covered by thin uncolored tissue. However, it is rather stiff.

joint tissue to fill the gaps between the arteries (fig. 4). In all performed angiographies, the bypass was demonstrated to be patent.

Histopathological Examination

The histological examination showed the proliferation of the smooth muscle cells and their migration to the intimal wall and the reepithelization of the inner side of the ePTFE as previously demonstrated [16]. A new vascularized adventitia covered the gaps and prevented bleeding. No collagen depositions were demonstrated. There was no evidence of vascular mural fibrinoid necrosis.

Discussion

Recently, the cerebral bypass operation has experienced a renewed awareness and recent papers indicate the need for technological innovation of this procedure [4, 8, 10, 11, 17, 18]. Furthermore, cyanoacrylates have been evaluated in the last decades as potential tissue adhesive for biomedical and surgical purposes [8, 13]. Previous forms of cyanoacrylate caused extensive tissue reaction, and thus could not be used as a tissue adhesive [12–14]. In the presented setup, we used an absorbable cyanoacrylate composed of 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate to improve the well-acknowledged ELANA bypass technique [13]. This sealant polymerizes to form a film that adheres to the tissue and/or synthetic material, creating a flexible physical seal that prevents leakage of blood. The function of this sealant is moreover mechanical and independent of the host coagulation cascade [12–14].

Our results show that the application of the adhesive glue in the ELANA procedure helps to reduce the number of necessary microsutures, to improve the necessary vacuum, to stabilize the arteriotomy procedure, to shorten the procedure time, and to reduce the postarteriotomy leaking. In fact, the technique may theoretically have some advantages: the procedure will be easier and quicker; the ring will be more stable with higher flap retrieval, and the glue is more flexible than the stitches.

The end-to-side anastomosis of type B and of type C has reached the best in vitro results. This may explain the assumption that the contact surface of the glue is more extensive with this technique. However, the application of the glue must be very localized and precise.

A salient issue in the application of the glue with the ELANA procedure is the evidence that the flap retrieval rate is higher than with suture alone and so this technique can have some potential advantages over the suture technique. The described microanastomosis technique was reliably repeated and functioned adequately in the majority of the experiments. The use of the ring should be continued. It is crucial to give stability to the shape or define the form of the connection and to have the possibility of repeatability. While the use of tissue adhesives might seem intuitive, improper selection and technique may result in suboptimal results. The potential tremendous thrombogenic and thromboembolic risk of accidentally intravasal penetration of the glue must be managed by careful handling of the glue. The thrombosis in 2 cases of this series indicates that the clinical application of this technique requires more laboratory and bioengineering investigations in order to improve the safety of the procedure. To rule out embolic contaminations, we suggest the use of a smaller tube obtained by cutting a 26-gauge intravenous cannula at the tip of the disposable dispenser.

Moreover, although this method seems to work well in an in vitro laboratory setup, in the experiments with animals the glue is rather stiff and hardens quickly. As a consequence, the clinical application may be problematic in intracranial procedures complicated by the depth of the craniotomy, the high working distances, the tiny spaces, the high angulations, and the cerebrospinal fluid flow. Additionally, the effects of cyanoacrylate on the neural tissues when infused into the subarachnoid space seem to be toxic [19], and more studies should be done to guarantee the safety of the procedure.

Conclusions

The merging of the ELANA technique with the recent advances in biomaterial engineering such as the 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate is an attractive alternative to give more stability and a better retrieval of the arterial wall flap after the arteriotomy in the laboratory in vivo and in vitro environment. However, the technical application in humans, although straightforward in the animal and in vitro setup, leaves some doubt, especially regarding the fast hardening of the glue, the humidity of the cerebrospinal fluid in humans, and the safety of neural cells.

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Disclosure Statement

Johnson & Johnson provided free of charge the sample vials of Omnex© used in all experiments. None of the authors had any financial interests in, received, or will receive any benefits or privileges of any kind from the companies mentioned in the paper.

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