Mesh Fixation Using a Cyanoacrylate Applied as a Spray Improves Abdominal Wall Tissue Repair

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A b s t r a c t

Background: Tissue adhesives are a feasible option to fix a hernia repair mesh, avoiding tissue trauma of suture fixation. Classically, they are applied in the form of a drop, although novel applications such as spray are emerging. This study compares the use of a new experimental cyanoacrylate (n-butyl) in the form of a spray or drops. *Materials and methods:* Three study groups of New Zealand White rabbits were established ($n \frac{1}{4}$ 6 each) according to the method used to fix a 5 3 cm polypropylene mesh in a partial abdominal wall defect model: control group (polypropylene stitches), adhesive drops group, and adhesive spray group. Morphological, immunohistochemical, and biomechanical strength studies were performed at 14 d postimplant. Collagen 1/3 gene ratio was determined by quantitative reverse transcription polymerase chain reaction.

Results: In the drops group, the adhesive obstructed the mesh pores and prevented tissue infiltration at the points of application. When the adhesive was applied as a spray, although more numerous, adhesive deposits were smaller and allowed for better host tissue infiltration into the mesh. The inflammatory response was similar in the adhesive groups and more intense than in the control group. Collagen 1/3 mRNA ratio was significantly higher in

the spray than the control group. The mechanical resistance of the meshes was similar in all three groups.

Conclusions: The application of the cyanoacrylate adhesive in the form of spray to fix polypropylene meshes in an animal model had a similar inflammatory response compared with droplet application. Neither application impacted the mechanical strength of the repaired area. An increased in collagen 1/3 ratio was found with cyanoacrylate spray compared with suture, and future studies should focus on this pathway.

Introduction

One of the many applications of tissue adhesives in surgery is their use to fix prosthetic materials for hernia repair.[1] To date, tissue adhesives of both biological (fibrin type)[2,3] and synthetic origin have been used. Among the latter, the most used are cyanoacrylates.[4,5] Inherniarepairsurgery,thetissueadhesivehas to stick a prosthetic material to the host tissue, thus avoiding the need for sutures.[6,7] Adhesives have several benefits over suturestitchessuchaseasyhandlingandrapidapplication,and they also avoid the trauma produced when a needle is inserted into the tissue, which is especially useful in patients receiving anticoagulation treatment. Other adverse effects related to the use of sutures that can be avoided, especially when meshes are fixed in the inguinal region, are entrapment of nerve endings, which in some cases explains the postoperative pain produced in patients undergoing hernioplasty.[8,9]

Because of their toxicity, the use of cyanoacrylates as tissue adhesives has generated some controversy. However, this toxicity has been overcome[10,11] by new long-chain chemical structures, which have been approved for use in human clinical practice.

To fix a mesh during hernia repair surgery, cyanoacrylates are usually applied as drops although spray or nebulizer formulations now exist. However, few studies have compared the two application modes, and existing studies have focused on the use of fibrin glues.[12,13] We hypothesized that spray could be an alternative to the current application of cyanoacrylates in the form of drops that would decrease the amount of adhesive in the recipient tissue and could improve the behavior of the tissue repair area.

In the present study, we designed an experimental *in vivo* trial to compare both ways of applying a new long-chained cyanoacrylate (n-butyl) in terms of its biological tolerance and the biomechanical strength provided. The prosthetic material selected for our study was polypropylene, as it is the most used biomaterial in the field of hernia repair. Depending on its structure and specifically on its porosity, the reticular meshes of polypropylene are divided into two types, the heavyweight (small pores) and the lightweight (large pores). Both types of meshes are used regularly in the clinic; however, some authors are still reluctant to use the large-pored prostheses because their difficult fixation with sutures to the recipient tissue because of its substantial porosity can compromise the disinsertion of the material. In this case, a heavyweight prosthesis (Surgipro; Medtronic, MN) was used.

Therefore, this study focused on checking if the fixation using cyanoacrylate in the form of spray in addition to the benefits already demonstrated over conventional sutures such as easy handling and rapid application and offered other advantages in terms of structural and mechanical quality of the repairneoformedtissueintheprocessofprostheticintegration.

Materials and methods

Surgical technique and study groups

Twelve New Zealand White rabbits of mean weight 3200 g were used. Animals were housed and handled according to European Union ethical directives for the treatment of laboratory animals (European Directive 2010/63/UE and European Convention of the Council of Europe ETS123). All procedures were approved by the Committee on the Ethics of Animal Experiments of the University of Alcala´ (Registration ES280050001165).

The samplesize in each groupof our study was determined by specialist staff in biomedical statistics that was consulted when we designed the original experiment.

For this study, numbers of animals were calculated so that results would be scientifically and statistically valid while keeping these numbers to a minimum and also avoiding unnecessary repetitions, attending to the principle of the "3 Rs" of animal used in the life sciences. This approach is required by law for animal research in the United States and Europe.

One hour pre- and 3 d post-operatively, animals received buprenorphine (0.05 mg/kg) (Buprecare; Divasa Farmavic, Barcelona, Spain) for pain relief. Anesthesia was induced through intramuscular injection of ketamine (70 mg/kg; Ketolar; Parke-Davis, Madrid, Spain), diazepam (1.5 mg/kg; Valium; Roche, Madrid, Spain), and chlorpromazine (1.5 mg/ kg; Largactil; Rhone-Poulenc, Madrid, Spain).

The abdominal skin was prepared and disinfected with povidoneeiodine before the procedure. Partial 5x3 cm defects were created in the ventral abdominal wall, comprising the anatomic planes of the internal and external oblique muscles.Transversemuscleandthe parietalperitoneum were spared. These defects were repaired using a polypropylene mesh (Surgipro).

Defects created on the right side of the abdominal midline were repaired by fixing the mesh, of the same size 5x3cm to the created defect, with an n-butyl cyanoacrylate adhesive (Safety Seal; Noricum,Madrid, Spain). In six of the animals, six adhesive drops (50 mL per drop) were placed at the four corners and in the middle of the longest edges of the mesh. In another group of six animals, the adhesive was sprayed evenly over the mesh from a 10 cm distance. Before using the adhesive, simple tests were carried out to be able to choose an equal spray application distance for all the implants. Three different measurements were tested: 5, 10, and 15 cm from the surface. It could be verified that by spraying the glue from a distance of 10 cm, the adhesive was most evenly distributed so that distance was established in all cases. The spray diffuser was loaded with 300 mL of adhesive, although the volume delivered was 175-200 mL.

For the control group, in six of the previous 12 animals, defects were created on the left side of midline, and the mesh was fixed by placing six 4.0 polypropylene stitches (Surgipro) at the four mesh corners and in the middle of the longest edges, as for the glue drops. On the free left side of the other six animals, the partial defect (PD) was created at the moment of animal sacrifice, without performing prosthetic repair, for use as a control in the biomechanical resistance study. This control group was designated PD. The tissue removed was discarded in all cases.

Skin incisions were closed using a running 3.0 polypropylene suture (Surgipro). According to the mesh fixation method, the study groups established were as follows:

- Drops (n ¼ 6): n-butyl cyanoacrylate drops
- Spray (n ¼ 6): n-butyl cyanoacrylate spray
- Control (n ¼ 6): monofilament polypropylene stitches

Fourteen days after surgery, the animals were euthanized, and the implant area recovered by excising the patch including adjacent host tissue around the margins. Implants plus surrounding tissue were collected and were cut into three 1.5 cm wide strips parallel to the shortest edges. The samples were cut into three 1.5 cm wide strips parallel to the shortest edges. The two end strips were used in the biomechanical tests, whereas the rest of the sample was destined for morphologic, immunohistochemical analysis and quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Morphologic and immunohistochemical analyses

For morphologic (light microscopy [LM] and scanning electron microscopy [SEM]) and immunohistochemical analyses, the strips of implanted mesh plus host tissue were processed using conventional histologic techniques as previously described.[14] Samples for histology were stained with hematoxylineeosin and Masson's trichrome.

For immunohistochemical staining, we followed the avidin-biotin-alkaline-phosphatase method using a monoclonal antibody for rabbit macrophages (RAM11; Dako, Agilent, CA). Nuclei were counterstained with hematoxylin.

The implant/tissue samples from histologic and immunohistochemical analyses were examined by LM (Zeiss Axiophot, Oberkochen, Germany) or SEM (ZeissDSM-950).

Immunohistochemical labeling was quantified through image analysis on at least 20 microscopic fields (200) of each sample in digitized photomicrographs using Image J software (https://imagej.nih.gov/ij/).

Collagen expression (qRT-PCR)

As described in our previous studies,[15] total RNA for qRT-PCR was isolated from implant tissue frozen at 80C using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocol. RNA was determined in a NanoDrop (ND-1000; Thermo Scientific, Wilmington, DE). Complementary DNA was synthesized using oligo dT primers (Amersham, Fairfield, CT) and the M-MLV reverse transcriptase enzyme (Invitrogen). qRT-PCR was performed in a StepOnePlus Real-Time PCR system (Applied Biosystems, Foster City, CA) using SYBR Green SUPER mix (Bio-Rad Laboratories, Hercules, CA). The housekeeping gene GAPDHR1 was used for sample normalization.

Rabbit primer sequences were as follows: collagen 1A2 (sense 50-ATG GTG GCA CCC AGT TTG AA-30 and antisense 50- AGG TGA TGT TCT GAG AGG CG-30), collagen 3A1 (sense 50- TGC TAA GGG TGA AGT TGG AC-30 and antisense 50CCG CCA GGA CTA CCA TTG TT-30), and GAPDH (sense 50-TCA CCA TCT TCC AGG AGC GA-30and antisense 50-CAC AAT GCC GAA GTG GTC GT-30). Results are expressed as the collagen
1/3 ratio.

Biomechanical strength tests

To test the biomechanical strength of the implants, an Instron 3340 Series tensiometer was employed (Instron, MA). Thirtysix tissue samples (two strips per defect) measuring 1.5 cm wide were prepared. Each strip comprising rabbit abdominal wall and the mesh implant was positioned vertically with the host tissue adjacent to the mesh margins secured inside the top and bottom pneumatic grips. On the free left side of six animals, a PD was created at the moment of animal sacrifice for use as a control in the biomechanical resistance study, PD control group. Twelve tissue samples (two strips per defect) measuring 1.5 cm wide were prepared in this group for the biomechanical study.

Tests were run until repaired area rupture at a rate of 5 cm/ min. The mean failure tension and stretch values were recorded, and the mean maximum strength values of the repair area obtained in each group and recorded in Newtons (N).

Data provided as means and their standard errors (standard error of the mean) obtained for each of the study groups (tensiometry, qRT-PCR, and macrophage count data) were compared using the ManneWhitney *U*-test. All statistical tests were performed using the GraphPad Prism 5 package (GraphPad Software, Inc, CA). Significance was set at *P* < 0.05.

Results

Macroscopic observations

At the end of the study period at 14 d postimplant, no signs of surgical site or mesh infection was observed in any of the three study groups. Neither was seroma or mesh detachment detected in any of the animals.

Morphologic and immunohistochemical analyses

In the control group (meshes fixed with polypropylene stitches), the mesh filaments were surrounded by collagen fibers. Blood vessels, fibroblasts, and inflammatory cells could be observed in the newly formed connective tissue around the biomaterial (Fig. 1A and D). To assess the inflammatory response to the implant, we determined RAM11 positive cells. These labeled inflammatory cells were found throughout the implant close to the mesh filaments (Fig. 2A).

Both LM and SEM microscopy images for the drops group revealed the tissue adhesive drops blocking host tissue infiltration in those areas. In the SEM micrographs, the tissue adhesive appeared dense and compact, without signs of absorption (Fig. 1B and E). Large numbers of macrophages and giant foreign body reaction cells were observed around the adhesive (Fig. 2B). In the implant zone that was free of adhesive, host tissue incorporation in the mesh was similar to that noted in the control group samples.

When the adhesive was applied in the form of a spray, different sized remains of adhesive could be observed throughout the whole area occupied by the Surgipro mesh. Host tissue incorporation appeared more homogeneous than in the drops group (Fig. 1C and F).
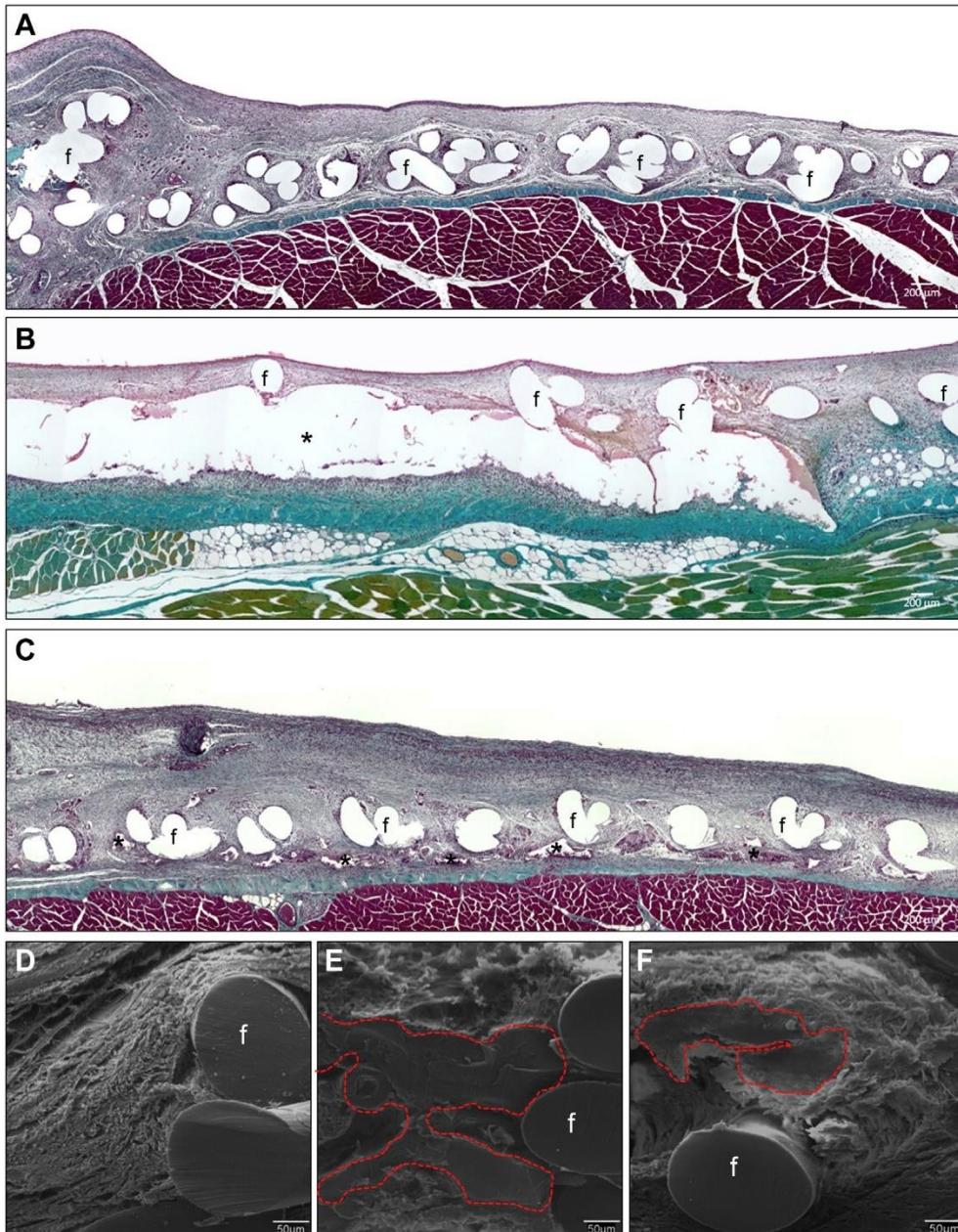
Fig. 1 e

Fig. 1- Representative panoramic histologic images of the host tissue response to the polipropileno implants with the three fixation methods (3100 magnification): stitches (A), adhesive drops (B), and adhesive spray (C). SEM microscopy detail (3200 magnification) of mesh implant in group fixed with stitches (D), group fixed with drops (E), and group fixed with spray (F). Cyanoacrylate could be observed between the filaments in drops and spray groups (red dashed line; f: mesh filament; *:cyanoacrylate).

Besides adhesive remains, it was possible to observe mesh filaments, macrophages, and giant foreign body reaction cells (Fig. 2C).

RAM11 positive cell percentages were slightly higher when the adhesive was applied as drops though compared with the spray, and the difference lacked significance. When compared with suture group, labeled cell proportions were significantly higher in both adhesive groups (Fig. 2D).
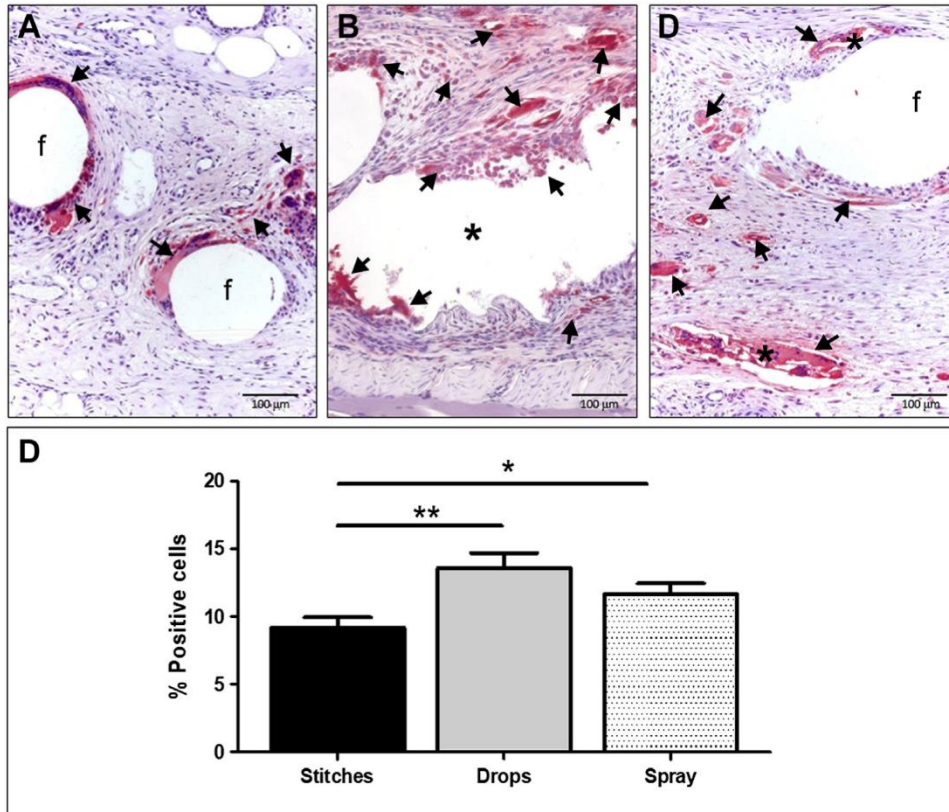

Fig. 2 - Immunohistochemical labeling with RAM11 antibody for macrophage detection (red color, arrows), after abdominal wall repair with a polypropylene mesh fixed with stitches (A), adhesive drops (B), or adhesive applied in form of spray (C). (D) Percentage of positive cells for all the study groups (3200 magnification) (*P< 0.05; **P< 0.005; f: mesh filament; *:cyanoacrylate).

Collagen expression (qRT-PCR)

To establish the maturation extent of the neoformed tissue, we analyzed the expression of the genes for collagens 1 and 3. The collagen 1/3 ratio was significantly higher for the spray group than control group, although no significant differences emerged between the spray and drops group or for the drops *versus* control groups (Fig. 3).

Biomechanical strength study

Mean biomechanical resistance of the PD group was 23.90 0.91 N. Mean biomechanical strength values recorded for the repaired area fixed in different ways failed to differ significantly among the study groups: control 35.46 1.33 N; drops 30.72 1.69 N; and spray 34.83 3.35 N. However, in all cases, there was a significant increase in these three study groups with respect to the PD ($P < 0.05$).
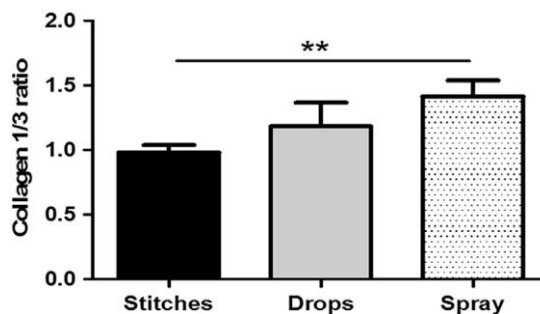

Fig. 3 -Collagen 1/3 mRNA ratio in the different study groups. The ratio was significantly higher in the spray than control group (**P< 0.005).

Load-stretch curves for each animal in the PD group and after abdominal wall repair with the polypropylene mesh fixed with stitches, adhesive drops, or adhesive applied in the form of spray 14 d after implantation are shown in Figure 4. The curves of the PD group showed less resistance to traction than the rest of the groups. Concerning to the group fixed with spray, the curves moved to the left of the graph, translating into a greater rigidity of the repaired area than the rest of the groups, although the forces reached were comparable to the rest of the repaired groups.

Discussion

In the field of hernia repair, an alternative to sutures for mesh fixation is the use of a tissue adhesive. Among these, the most widely used are fibrin glues[16] although there has been a recent surge in the use of new synthetic tissue adhesives including cyanoacrylates.[17] Advances in these recently introduced cyanoacrylates have involved modifications to their structure (mainly chain lengthening), which has made them perfectly biocompatible and useful for internal use.[18] So far, the general consensus is that the fixation of prosthetic materials with tissue adhesives for hernia repair is faster and leads to a similar hernia recurrence rate to that provided by the suture method.[5,19] Controversy, however, exists with regard to postoperative comfort especially in terms of pain both immediately after the surgery and chronic pain. In some studies, the use of a tissue adhesive has been related to reduced postoperative pain[20,21] while other authors report no differences in patient comfort between the two fixation methods.[6,22]
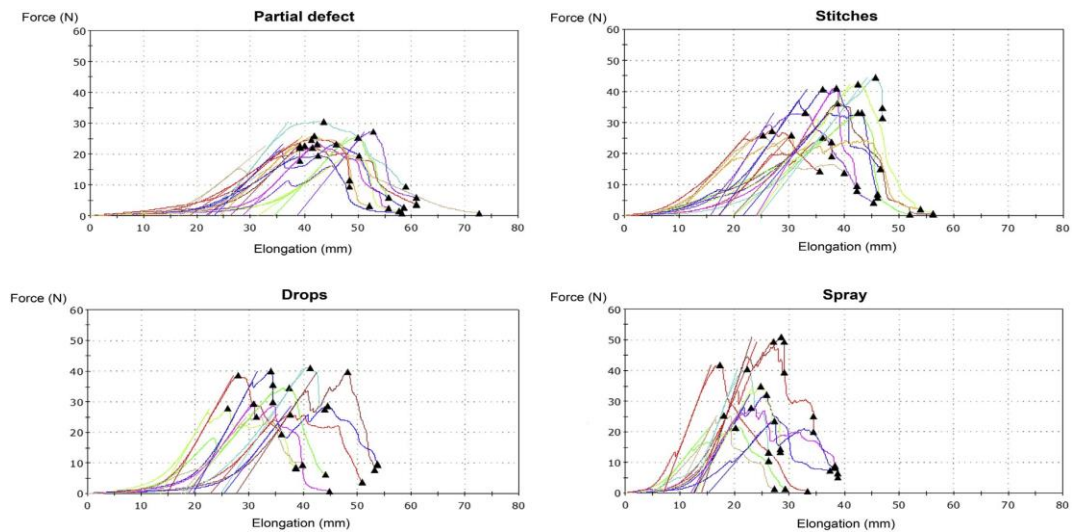

Fig. 4- Load-stretch curves for each animal in the PD group and after abdominal wall repair with the polypropylene mesh fixed with stitches, adhesive drops, or adhesive applied in form of spray, 14 d after implantation. Load is represented in newtons and elongation in millimeters.

In this study, we used the New Zealand White rabbit as the experimental animal, with which our research group has broad experience.[23] The biomaterial selected was heavyweight polypropylene, as this material is commonly used in human clinical practice, and the tissue adhesive tested for mesh fixation was an experimental cyanoacrylate (n-butyl). The objective of our study was to compare the form of adhesive application, as drops or spray. Cyanoacrylate adhesives are usually applied as small drops, yet fibrin glues are recently being used as sprays. The study was designed to check whether host tissue incorporation into the implanted mesh would not be modified and also to confirm if the mechanical strength obtained in the repair zone would be similar for both application modes. The study period selected was 14 d as we wanted to examine the early host tissue incorporation process after fixing the meshes with cyanoacrylate.

Another issue we considered was the optimal spray distance for applying the tissue adhesive. In line with the 5-8 cm distance recommended by Brand *et al.*[12] for spraying a fibrin glue, we found that by spraying from a distance of 10 cm, the adhesive was most evenly distributed.

Our morphologic observations in the mesh tissue integration study served to identify differences according to the final distribution of the cyanoacrylate adhesive. Thus, when applied as a spray, the mesh pores were not obstructed as occurred when drops of adhesive were used to fix the mesh. In our LM and SEM photographs, it may be seen that when applied as a spray, the adhesive is deposited in small zones between the mesh filaments, whereas the drops of adhesive fully occupied the interfilament zones at the points of application avoiding any host tissue ingrowth in these zones.

The amount of tissue adhesive that remains in the repair zone determines the inflammatory reaction produced in the host. If a large amount of adhesive is used, this can increase the magnitude of this response accompanied by reduced strength and greater tissue stiffness.[16] According to Losi *et al.*,[24] the wound repair process is improved if smaller amounts of tissue adhesive are used. Effectively, the use of a spray led to a lower amount of fibrin glue deposited on the mesh in an *in vitro* study performed by Brand *et al.*[12] This mode of applicationwas found to avoid blocking the mesh pores and thus gave rise to more effective host tissue incorporation besides the benefit of leaving behind less residual glue, improving its reabsorption by the organism.

We observed no significant differences in macrophage cell percentages. This is because when applied as drops, the adhesive is restricted to individual zones, whereas in the case of the spray, it is spread out throughout the scar tissue. In this last situation, although there were numerous zones of inflammation, these were small, which could lead to the improved absorption of the adhesive in the mid or long term.

Tissue repair processes consist of three overlap phases (inflammatory, proliferative, and remodelingematuration), which occur after tissue lesion with the aim of restoring the damaged tissue. Collagen deposition is very important because it increases the strength of the repaired area. Type 3 collagen and fibronectin generally begin to be produced in great amounts in the neoformed connective tissue at proliferation stage, and they are the main tensile components until the later phase of maturation, in which they are replaced by the stronger type 1 collagen.

Collagen 1/3 mRNA ratio was higher in the adhesive groups than the control group, although differences were only significant when we compared the spray application and the control group. This is likely attributable to a more advanced wound repair process in the groups using cyanoacrylate spray instead of sutures. The greater ratio recorded when the meshes were fixed using the spray indicate that fibroblasts in the newly formed tissue around the mesh filaments show the greater gene expression of collagen type 1 relative to type 3, what it would mean a greater synthesis and deposition of mature collagen type 1 protein in the extracellular matrix of this repair connective tissue to the detriment of the more immature, reticular type 3 collagen, thus conferring density and strength to the neoformed tissue in the repair zone. In the case of the group fixed with drops, the more intense unresolved inflammatory process shown in Figure 2 is going to be related to a delay in the reparative process and consequently in a lower ratio of col 1/3.

Another important aspect to consider is the absorption time of the cyanoacrylate adhesive used to fix the meshes. In prior long-term studies of our group,[15] we observed that the volume of adhesive applied as drops was still present 180 d after mesh implant. We hypothesize that this absorption time could be shorter for the spray, but longer term studies would be necessary to address this issue. The adhesive will initially act as a permanent fixing material;

however, as the adhesive is being absorbed, it will be replaced by repair tissue that will be integrated with the mesh and will contribute to the biomechanical characteristics of the repaired area.

Our mean biomechanical strength data indicated similar behavior recorded for the meshes fixed in different ways, that in all cases showed significant differences with respect to the PD group. Notwithstanding, the strengths recorded in the spray group more resembled control values for the suture fixation method. Load-stretch curves showed greater rigidity of the repaired area in the spray than the rest of the groups, although the forces reached were comparable to the rest of the repaired groups.

Both in an *ex vivo* study [15] and an *in vitro* study,[26] it was found that cyanoacrylates showed lower biomechanical strength than fibrin glues and thus do not seem to offer as good results as the more conventional fixation methods.[25] In a study by Ladurner *et al.*,[27] a lower biomechanical resistance was obtained for meshes fixed with a cyanoacrylate adhesive than for the use of sutures or tackers. In the present study, we observed no difference in biomechanical strength when we compared the use of sutures with that of the tissue adhesive, regardless of the application method. If we consider that the drops method uses a much larger quantity of adhesive and that sutures do not offer any additional resistance being a much more aggressive fixation method, the use of a spray could provide the benefits of the same final strength, the use of a minimum amount of adhesive, and an absence of tissue trauma. The latter could help explain our polymerase chain reaction results for collagen expression whereby the spray method gave rise to the higher collagen 1/3 mRNA ratio translating to a more mature neoformed tissue, which could confer additional resistance to the repair zone. These observations are consistent with those of other authors[28] who compared the biomechanical strength of an n-butyl cyanoacrylate with that of sutures in a mesh tissue repair model.

The limitations of our study include the experimental model in the rabbit, which could show different biological behavior. However, the good tissue tolerance shown so far by these adhesives in both experimental and clinical situations suggests their possible applications in human clinical practice.

Conclusions

The application of the cyanoacrylate adhesive in the form of spray to fix polypropylene meshes in an animal model had a similar inflammatory response compared with droplet application. Neither application impacted the mechanical strength of the repaired area. An increased in collagen 1/3 ratio was found with cyanoacrylate spray compared with suture, and future studies should focus on this pathway.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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