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ORIGINAL ARTICLE

In vitro study of the optimum volume ratio of activator to adhesive in gelatin-resorcin-formalin glue

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Abstract
Objective. Excessive use of activator (formaldehyde + glutaraldehyde) may cause late complications after use of gelatin-resorcin-formalin (GRF) glue during surgery. The goal of the study was to define the appropriate ratio of activator to adhesive and to establish an approach for accurate control of this ratio.
Methods. The relation between adhesive force and the activator/adhesive ratio was studied by attaching two sheets of equine pericardium using GRF glue, with ratios from 1:50 to 1:2. The amount of activator was measured per drip from the needle in the GRF glue kit and other needles (27, 25, 23, 22, and 21 gauge).
Results. The adhesive force was about 400 gram-weight (gw) for activator/adhesive ratios from 1:50 to 1:20. This force showed a significant increase to 1317 ± 462 gw for a ratio of 1:10 compared to the force at a ratio 1:20 ($P = 0.0069$) but did not increase significantly for ratios above 1:10. The activator volume was 12.5 μl in one drip from the needle in the GRF glue kit and 4.3 μl in one drip from the 27-gauge needle. Therefore, the 27-gauge needle is suitable for measuring the activator volume.
Conclusion. In vitro, an activator at a ratio of one-tenth the volume of the adhesive provides approximately maximum force; any more activator is residual and potentially harmful. Measurement of the activator volume using a 27-gauge needle and the adhesive volume using a syringe is recommended to control the ratio accurately.

Key words Gelatin-resorcin-formalin glue · Activator · Adhesive · Acute aortic dissection · Postinfarction ventricular septal defect

Introduction

Excessive use of activator (formaldehyde + glutaraldehyde) may lead to the late complication of pseudoaneurysm formation or redissection after the use of gelatin-resorcin-formalin (GRF) glue during surgery for acute aortic dissection as residual aldehyde is harmful to surrounding tissue.[1] The manufacturer's information indicates that an activator/adhesive ratio of 1:40 to 1:10 is appropriate. However, only one study has investigated the ratio of the activator to the adhesive (gelatin + resorcin) and the effects of residual formaldehyde.[2] Therefore, the first goal of this study was to define the optimal ratio. The second goal was to establish a method to control the activator/adhesive ratio in clinical settings as the commercial kit does not have a suitable tool for measuring the amount of adhesive or activator. Here, we report a procedure to replicate the optimal ratio in a clinical setting by accurate measurement of the adhesive and activator volumes.

Materials and methods

Two sheets of commercially available equine pericardium were prepared to examine the relation between adhesive force and the activator/adhesive volume ratio.

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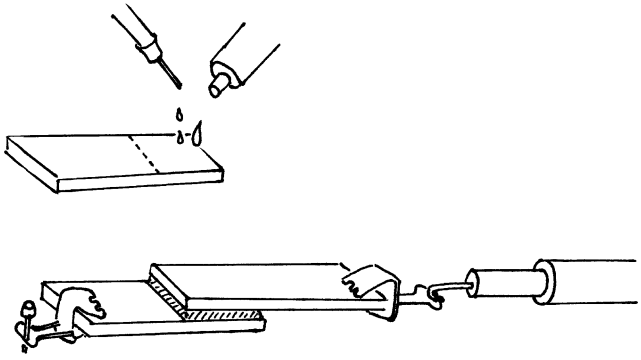

Fig. 1 The experiment

The two sheets of pericardium were 1 × 3 cm in size, and areas of 1 × 1 cm at the ends of the sheets were used as adhesive areas, with the other ends were pulled by a binder clip connected to a tension gauge (product no. 75038; Shinwa Sokutei KK, Sanjo, Niigata, Japan) (Fig. 1). The volume of adhesive was fixed at 0.2 ml, and various amounts of activator were added to give activator/adhesive ratios of 0.02, 0.025, 0.033, 0.05, 0.10, 0.20, 0.33, and 0.50. The adhesive and activator were mixed for 1 min, after which the two sheets of pericardium were pressed together using fingers for 4 min. The adhesive tension was determined 5 min later by measuring the maximum tension just before breaking of the adhesion. The measurements for each ratio were performed six times. The temperature of the glue was maintained at 40°–50°C, and the pericardium was left at room temperature.

The amounts of activator per drip from the needle in the GRF glue kit and from commercial needles of 27, 25, 23, 22, and 21 gauge were determined by measuring the number of drips required to make a volume of 1 ml. Measurements were performed six times for each needle.

Data are shown as the means ± standard deviations. Student's *t*-test was used to compare values of tension, with $P < 0.05$ taken to indicate a significant difference.

Results

The mean maximum tension was about 400 gw for activator/adhesive ratios from 1:50 (0.02) to 1:20 (0.05) (Fig. 2). The maximal tension was 1317 ± 462 gw at a ratio of 1:10 (0.1), approximately three times the tension of 437 ± 174 gw at a ratio of 1:20 (0.05), with a significant difference in tension between these activator/adhesive ratios ($P = 0.0069$). The tension did not show further significant increases at ratios above 1:10 (Fig. 2).

The activator volume in one drip from the needle in the GRF glue kit was 12.5 µl (Table 1). Smaller needles provided a smaller amount of activator per drip, with 4.3 µl in one drip from a 27-gauge needle.

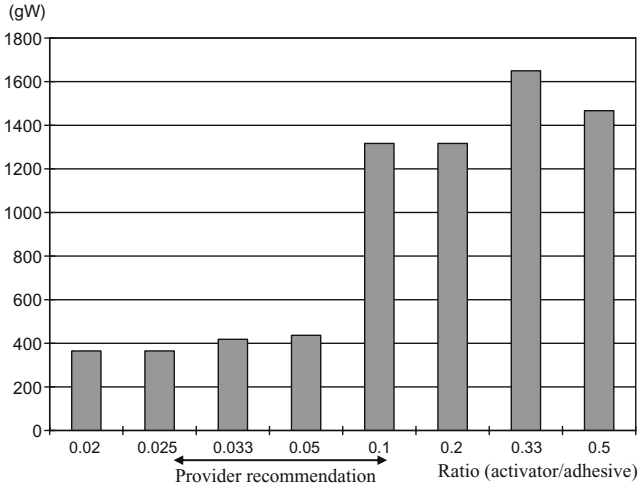

Fig. 2 Mean maximum tension (gram-weight, gw) for various activator/adhesive ratios

Table 1 Activator volume in a drip from each needle

Needle size	Drip volume (µl)
Needle in GRF glue kit	12.5
21 Gauge	10.7
22 Gauge	8.1
23 Gauge	7.3
25 Gauge	5.0
27 Gauge	4.3

Discussion

The GRF glue has an adhesive force that is seven times stronger than that of fibrin glue for attaching biological tissues.[2] The value of GRF glue is well established in aortic surgery[3] and postinfarction ventricular septal defect repair,[4] but a recent report showed pseudoaneurysm formation during long-term follow up.[5] In contrast, use of GRF glue during acute aortic dissection surgery with felt reinforcement and a minimal dose of activator does not seem to cause long-term tissue degeneration.[1]

The first goal in this study was to determine the optimal volume ratio for the activator and adhesive. The instructions in the current GRF kit indicated that an activator/adhesive ratio of 1:40 to 1:10 should be used, and earlier data from the distributor indicated that a volume ratio of 1:10 was optimal.[6] Our data showed a significant difference in maximal tension between activa-

tor/adhesive ratios of 1:20 and 1:10, but no further increase in tension at ratios over 1:10. Therefore, we believe that an activator/adhesive volume ratio of 1:10 is sufficient to crosslink most side chains of the gelatin protein in the adhesive and that excess activator is residual at the surgical site and may result in degeneration of surrounding tissue. We note that our measurement of maximal force was made 5 min after mixing the activator and adhesive, and the chemical reaction should continue for 11 min.[6] Therefore, a smaller amount of activator than that in the 1:10 mixture may produce more force than was observed in our measurement. However, in a clinical setting of cardiac arrest, a period of 5 min between procedures may be more realistic; and our results suggest that under such conditions use of an activator/adhesive ratio of more than 1:10 results in residual activator with no improvement in adhesion.

Because adhesive is supplied in an aluminum tube in the GRF kit, we cannot measure an accurate amount of adhesive. A 1-ml syringe was used to deliver an accurate amount of adhesive to the target area in this study. In a clinical setting, we use a 5-ml syringe to introduce adhesive to the surgical site. We recommend refilling the adhesive into the syringe from the aluminum tube and keeping the syringe in a warm bath to maintain the adhesive within a limited temperature range. Accurate measurement of the activator is also a concern. One drip from the needle in the GRF glue kit is stated in the instructions to have a volume of 15 μl, but our data indicated a volume of about 13 μl per drip. Regardless of the exact volume, the size of the needle in the kit is too large for fine adjustment to obtain the optimal activator/adhesive ratio. During repair of a dissected aortic root, we normally use a single volume of adhesive of 100–400 μl (0.1–0.4 ml) and repeat the adhesion procedure two or three times. Therefore, the optimal activator/adhesive ratio of 1:10 requires measurement of 10 μl of activator for 100 μl of adhesive, and the needle in the GRF kit is too large for this purpose. We tested several other needles and found that a 27-gauge needle had an associated volume of about 4 μl per drip, which allows for fine adjustment of the volume of activator required to obtain the optimal activator/adhesive ratio.

Pseudoaneurysm formation or redissection has been reported after use of GRF glue[5] and has been linked to excess formalin, which has caused some surgeons to stop using GRF glue. However, it is unclear if GRF glue should be abandoned because it also has potent hemostatic properties. We believe that GRF glue has both benefits and risks, but we suggest that proper use of GRF glue with an activator/adhesive ratio of 1:10 and cautious use of felt reinforcement can eliminate or reduce the risk of pseudoaneurysm. Recently, the distributor has reduced the amount of activator in the kit from 5 ml to 1 ml. Because 15 ml of adhesive is included in the kit, we strongly recommend that at least 1.5 ml of activator should be included; otherwise, only 10 ml of adhesive can be used for our recommended ratio. We emphasize that the surgeon should take great care when using GRF glue as a tool as it has both benefits and risks.

Conclusion

In vitro, an activator/adhesive volume ratio of 1:10 for GRF glue provides an approximately maximal adhesive force. More activator did not increase the adhesive force, and the residual activator may be harmful. For accuracy, we recommend measuring the adhesive volume using a syringe and measuring the activator volume using a 27-gauge needle.

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