Recent status of gelatin-resorcin-formalin glue for acute type A aortic dissection

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Gelatin-resorcin-formalin (GRF) glue was developed by Braunwald and Tatroles in 1964. Initially, it was mainly used as a hemostatic agent by gastrointestinal surgeons and urologists.¹ In 1977, Bachet et al.² used GRF glue as an adhesive and hemostatic material for aortic surgery and reported that it was very useful. The use of GRF glue dramatically improved the outcomes of surgery for Stanford type A acute aortic dissection, previously associated with high mortality due to frequent intraoperative bleeding from the fragile aortic wall tissue. Shimono et al.^{3,4} reported that the introduction of GRF glue markedly improved surgical outcomes, decreasing the in-hospital mortality to 6.7%. In surgery for acute type A aortic dissection, GRF glue decreases the risk of bleeding by holding together and reinforcing the dissected aortic wall during the acute phase and preventing bleeding from suture sites. The study of Isoda et al.⁶ focused on the former effect.

The formalin component of GRF glue promotes polymerization of gelatin-resorcin, resulting in a three-dimensional network. This network underlies the adhesive strength of GRF glue.⁵ Clinically, however, there is currently no standardized component ratio for GRF glue, and different formulations are used. Because formalin is toxic to tissue, the minimum concentration required for effective adhesion should be used. Isoda

et al. showed that an activator/adhesive combination ratio of about 0.1 is minimally required to produce the highest adhesive effect.⁶ This finding might be useful for decreasing the amount of formalin. To assess adhesive strength, Kuniyama et al. evaluated the degree of GRF polymerization for an activator/adhesive ratio ranging from 0 to 0.1. They similarly found that a ratio of 0.1 resulted in the greatest polymerization and highest adhesive strength.⁵

However, even when used at the lowest combination ratio required for maximum adhesive strength, formalin can still potentially damage tissue. Such damage is not appreciable during the early postoperative period. Suzuki et al. reported the development of false aneurysms at the aortic root 30 months after initial surgery, on average.⁷

Fukunaga et al. reported on clinically induced tissue injury related to the use of formalin in 1990. In all, 7 (6.4%) of 109 patients who tolerated surgery with the use of GRF glue required reoperation after 22.6 months, on average, for redissection of the aortic root attributed to the use of GRF glue at initial surgery.⁸ Bingley et al. performed reoperation for redissection of the aortic root in 12% of patients 33 months after initial surgery, on average.⁹ Redissection of the aortic root was reported to occur at an incidence of 7% by Kazui et al.,¹⁰ 64% by Von Opell et al.,¹¹ and 50% of 50 patients by Nakajima et al.¹² Nakajima et al. used GRF glue prepared by adding only 2 to 3 drops of formalin to 1 ml of gelatin-resorcin, as recommended by Bachet et al.,² in the last 16 patients of a series but reported that redissection occurred at a high rate (37%) during the late stage.¹² Suzuki et al. reported that false aneurysms associated with dehiscence of the proximal suture line developed in 31 of 193 survivors among 221 patients with acute type

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A dissection accompanied by false aneurysms who underwent surgery with the use of GRF glue.⁷ Formalin was added in 0.04-ml drops with the use of a small syringe. Three to five drops of formalin (0.12–0.20 ml) were added to 3–5 ml of gelatin-resorcin (activator/adhesive ratio = 0.04). Microscopic examination of the tissue to which GRF glue was applied revealed medial degeneration and disappearance of the nuclei of medial smooth muscle cells. These findings suggested that GRF glue can cause degeneration and necrosis of the media even if the activator/adhesive ratio is within appropriate limits.

Some reports have claimed that midterm and long-term complications associated with GRF glue can be prevented by proper use. Bachet et al.^{1,2} reported that no aortic lesions were caused by GRF glue during 20 years of experience, and Shimono et al.^{3,4,13,14} found no evidence of cytotoxicity or tissue necrosis, although reoperation was performed for redissection caused by GRF glue in 1 of 138 patients who underwent surgery. Shimono et al. reinforced the aortic stump with Teflon felt after applying GRF glue to the dissected aortic wall, whereas Fukunaga et al.,⁸ Von Oppell et al.,¹¹ Nakajima et al.,¹² and Suzuki et al.⁷ did not. The use of Teflon felt reinforcement might thus lower the incidence of redissection and false aneurysms during the late stage.

Even if no clinical evidence of tissue damage is apparent, GRF glue may still injure tissue. This is another reason the use of GRF glue should be discontinued as soon as a new surgical procedure is shown to have early outcomes equivalent to those of surgery with the use of GRF glue.

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