Prevention vs. Cure: is BioGlue priming the optimal strategy against E-Vita Neo graft oozing?

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Abstract

Background Since the introduction of the E-Vita Open NEO aortic prosthesis in 2020, several incidences of post-anastomotic oozing from the polyester portion of the graft have emerged. The use of BioGlue to prime E-Vita Open NEO to prevent this has been suggested as a way to mitigate this worrying complication. We investigate the extent of graft oozing in E-Vita Open NEO and evaluate the use of BioGlue in preventing oozing, both experimentally and in terms of potential clinical complications. Methods and materials E-Vita Open NEO (in straight and branched configurations) was implanted in a perfused model. The distal stent-graft and side branches were clamped, and the graft pressurised with blood to 120 mmHg. The volume of blood (ml) oozing from the graft within 60 seconds was measured. Non-pressurised grafts were coated with BioGlue up to a thickness 1-, 2-, and 3 mm, and the volume (mm3) of BioGlue required to do so was recorded. Results Within 60 seconds, 250.0 ml of blood oozed from the grafts tested. 43.694 mm3, 87.389 mm3, and 174.778 mm3 of BioGlue was required to coat the device with 1-, 2-, and 3 mm of BioGlue. Conclusion Graft oozing from E-Vita Open NEO represents an omnipresent and worrying risk. The use of BioGlue herein is likely associated with several adverse consequences, which are an additional risk on top of that posed by graft oozing. These risks call into question the suitability of E-Vita Open NEO, especially when compared to alternative devices not affected by oozing.

Prevention vs. Cure: is BioGlue priming the optimal strategy against E-Vita Neo graft oozing?

Running title: BioGlue for FET Oozing

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ABSTRACT

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Methods and materials

E-Vita Open NEO (in straight and branched configurations) was implanted in a perfused model. The distal stent-graft and side branches were clamped, and the graft pressurised with blood to 120 mmHg. The volume of blood (ml) oozing from the graft within 60 seconds was measured. Non-pressurised grafts were coated with BioGlue up to a thickness 1-, 2-, and 3 mm, and the volume (mm^3) of BioGlue required to do so was recorded.

Results

Within 60 seconds, 250.0 ml of blood oozed from the grafts tested. 43.694 mm^3, 87.389 mm^3, and 174.778 mm^3 of BioGlue was required to coat the device with 1-, 2-, and 3 mm of BioGlue.

Conclusion

Graft oozing from E-Vita Open NEO represents an omnipresent and worrying risk. The use of BioGlue herein is likely associated with several adverse consequences, which are an additional risk on top of that posed by graft oozing. These risks call into question the suitability of E-Vita Open NEO, especially when compared to alternative devices not affected by oozing.

1. BACKGROUND

Surgical glue has been a familiar component of the surgeon's armamentarium since the 1990s, and is used as an adhesive or adjunct across nearly all surgical specialties.[1] Of the several commercially available options, BioGlue (CryoLife Inc., Kennesaw, GA, USA) has enjoyed particularly widespread use among cardiothoracic and vascular surgeons, after it gained FDA approval for use as a haemostatic adjunct in cardiovascular surgery in 2001.[1] Its indications were then extended to entail aortic aneurysm surgery, and in particular aortic arch surgery. Observation studies have delineated its adjunctive use to vascular anastomosis, which yielded reduced intraoperative and postoperative bleeding, and overall length of stay in cases of aortic dissection.[2,3]

However, the use of BioGlue has also been associated with toxicity, embolic risk, impaired aortic growth, myocardial and nerve damage, pseudoaneurysm formation, cardiac tamponade, inflammation, and necrosis.[1,4-6] Enthusiasm for the use of surgical adhesives for AD has reportedly diminished over concerns of these additional risks.[6] Notably, CryoLife also warn against exposure of intracardiac structures, circulating blood, and nerves to BioGlue, as well as against its application in excess.[7]

In a recently published report, Ho et al. outline a potential new application of BioGlue in total arch replacement.[8] Out of concern for excessive oozing from the polyester graft segment of the E-Vita Open NEO hybrid prosthesis (CryoLife Inc., Kennesaw, GA, USA), BioGlue was used to prime the graft fabric between completion of anastomoses and resumption of blood flow. Satisfactory haemostasis was reported

achieved following the use of two vials of BioGlue (for priming) and thromboelastography (TEG)-guided blood product transfusion.[8]

The suggested use of BioGlue as a pre-emptive safeguard against graft oozing is particularly intriguing and seeks to prevent catastrophic bleeding that may occur during E-Vita Open NEO implantation in the absence of any technical error.[8,9] Indeed, the propensity for the polyester segment of E-Vita Open NEO to ooze excessively once blood flow is resumed is an extremely concerning flaw; with multiple cases reported in literature following its introduction in 2020.[9] It is thought that the lack of gelatine and collagen impregnation greatly increases the porosity of the E-Vita Open NEO graft, and that patient-specific haemodynamic factors may further augment the risk of oozing.[8,10]

Ho and colleagues' report advocating the use of BioGlue priming to prevent E-Vita Open NEO graft oozing highlights several unanswered questions and areas for further research.[8] Namely, in addition to the sequelae associated with graft oozing, what further risks does priming the outer surface of the arch prosthesis with BioGlue introduce? Are both additional risks justified by improved performance associated with E-Vita Open NEO, in comparison to existing market alternatives (in which oozing has hitherto not been reported)?

With these issues in mind, our investigation seeks to elucidate the extent of graft wall porosity in E-Vita Open Neo and the amount of BioGlue needed to prevent oozing, with a view of evaluating the safety and efficacy of BioGlue priming as a preventative strategy.

2. METHODS AND MATERIALS

In a clinical research laboratory setting, the E-Vita Open NEO hybrid prosthesis was tested in a perfused thoracic model to assess its propensity for oozing, and subsequently, the efficacy of BioGlue for preventing oozing. E-Vita Open NEO was tested in both its straight and branched configurations. Device dimensions are summarised in Table 1. Ethical review and approval, or written informed consent for participation were not required for the study in accordance with local legislation and institutional requirements.

The E-Vita Open NEO device was fully perfused within an experimental thoracic model, replicating as close as possible the real-life surgical scenario. The distal stented segment and all four side branches were clamped distally. The graft was then pressurised to 120 mmHg with human blood (from blood packs) from the proximal end until full, at which point the inflow valve was closed and the volume of blood in (ml) leaking from the graft wall was measured for 60 seconds. Subsequently, the volume (mm^3) of BioGlue required to cover the outer surface of E-Vita Open NEO (28mm and 30mm), up to thicknesses of 1.0, 2.0, and 3.0 mm, was measured. This aspect was measured while the prosthesis was not filled or subject to endoluminal pressure to replicate the conditions in which Ho et al. recommend priming the graft with BioGlue (after anastomosis and prior to resumption of blood flow).[8] The priming technique depicted by Ho et al. was used.

3. RESULTS

3.1 Graft Oozing

The dimensions of the prostheses used for testing are summarised in Table 1. Following full pressurisation of the prosthesis, blood oozing was immediately noted. A blood stream (Figure 1) was noted 30 seconds after peak pressure was reached. By 60 sec, a heavy stream of blood oozing from the graft was noted (Figure 2). Oozing was also noted along the graft branches. For each device, in total 250.0 mL of blood oozed through the prosthesis wall within 60 seconds.

3.2 BioGlue Priming Volume

Impregnating E-Vita Open NEO with a 1-, 2-, and 3-mm coat of BioGlue, whilst not pressurised and using the technique depicted by Ho et al., required 43.694 mm^3, 87.389 mm^3, and 174.778 mm^3 of BioGlue respectively.

4. DISCUSSION

Oozing from the polyester segment of the frozen elephant trunk (FET) prosthesis is undoubtedly a worrying and potentially catastrophic challenge that seemingly may occur in the absence of technical error. Alarmingly, Ho et al. note that such a complication should be 'expected' during implantation of E-Vita Open NEO.[8] Figures 1 and 2 depict visually the extent of the oozing that may occur – within 30 seconds of pressurisation, oozing was sufficient for streams of blood along the outer surface of the graft to form, and eventually 250 mL of blood was lost within 1 min of pressurisation. Subsequent investigations revealed that a considerable amount of BioGlue was required to impregnate the entirety of E-Vita Open NEO. Impregnation of a 1 mm coat of BioGlue required 43.694 mL of BioGlue (amounting to five 10 mL syringes) while the graft was not under tensile stress. It would be reasonable to suggest that a greater volume yet of BioGlue would be needed to coat a fully expanded FET graft of this type. For reference, the amount of BioGlue applied in cases such as aortic root replacement, graft-aorta anastomosis etc. rarely exceeds 5 mL.[11]Priming of E-Vita Open NEO to prevent oozing therefore demands far more BioGlue than usual.

4.1: Graft Oozing

It is worth emphasising that oozing from the graft portion of E-Vita Open NEO is not a phenomenon unique to Ho et al. Rather, it is a well-documented complication associated with use of the device that surgeons, as pointed out by Ho et al., should expect rather than simply be aware of.[8,10] In their study detailing initial experiences with E-Vita Open NEO in the Asia-Pacific region, Jakob et al. highlight a case of graft oozing during FET surgery in a 54-year-old male with ascending aortic aneurysm and type B aortic dissection.[10] Oozing from the polyester segment persisted following protamine administration and CPB weaning, and eventually required liberal amounts of Surgicel® Fibrillar™ (Johnson and Johnson N.V., Belgium) with pressurised packing for several minutes to be controlled.[10] Further, Czerny et al. also highlight three cases of profound graft oozing during E-Vita Open NEO implantation, following CPB weaning and protamine administration.[9] Routine substitution of plasmatic and cellular coagulation, guided by thromboelastometry, was unsuccessful in controlling graft oozing. One patient required 23U of red blood cells, 28U of fresh frozen plasma, and 16U of thrombocytes within the first 24 hours postoperatively. All three patients had complicated postoperative courses, involving low cardiac output necessitating inotropes, haemodialysis, multi-organ failure, paraplegia, and death.[9] A recent systematic review by Bashir et al. also concluded that reports on post-FET coagulopathy were associated with substantially higher heterogeneity in E-Vita Open NEO® and Cronus® compared to Thoraflex® and Frozenix®.[12] It is possible that reports on perioperative coagulopathy associated with E-Vita Open NEO® would encompass cases wherein graft oozing lead to a need for increased blood product transfusion, or reintervention to correct bleeding.[12]

The risk of graft oozing in FET for TAR is likely governed by surgical and non-surgical factors. Modern surgical techniques, low graft porosity, advanced suture material, and anastomotic adjuncts used to support suture lines (e.g., BioGlue) all serve to greatly diminish the likelihood of graft oozing. In contrast, the lack of gelatine and collagen impregnation in E-Vita Open NEO has likely re-introduced the risk of graft oozing due to massively increased graft porosity.[9] This is unsurprising considering there have hitherto been no reports of graft oozing from market equivalents (i.e. Thoraflex®, Frozenix®, and Cronus®) that do feature gelatine and collagen impregnation. Non-surgical factors, such as routine use of thromboelastometry, allow continued monitoring of the patient's intraoperative thrombotic state and enables rapid intervention against aberrant haemodynamics or coagulopathy.[9]Interestingly, Ho et al. point out that graft oozing mostly occurred in patients presenting with abnormal TEM findings.[8] It is unclear why E-Vita Open NEO® is not impregnated with collagen or gelatine, especially considering this seems to be a standard feature in similar commercially available devices, and that abnormal thrombotic states are not rare pre-operative characteristics in patients undergoing aortic surgery.

4.2: Is BioGlue priming to prevent graft oozing safe?

The exposure of lysine molecules presents in both the BSA component and the ECM of the target tissue to the glutaraldehyde component of BioGlue results in the formation of covalent bonds between lysine molecules; this creates a strong scaffold to reinforce anastomoses, and to aid close of the false lumen (FL).[11] In this regard, BioGlue is a profoundly useful tool: 65% of its final binding power is reached within 20 seconds, and

maximal strength is reached within two minutes, regardless of temperature or exposure to water.[11] BioGlue has been associated with reduced anastomotic bleeding, as well as reduced total blood loss, circulatory arrest duration, procedure duration, and overall length of stay.[1] Typically, 5 mL is sufficient for most applications in cardiac and aortic procedures.[11]

Ho and colleague's method for priming the FET prosthesis with BioGlue prior to resumption of blood flow is straightforward and involves application of the glue to the outer surface of the graft using the delivery syringe.[8] Two vials of BioGlue were reportedly used for fabric priming, however slight, residual (albeit potentially benign) oozing from the graft persisted once blood flow resumed.[8] Priming reportedly allowed the patient to be safely weaned off CPB with a systolic blood pressure of 120 mmHg.[8]

At this juncture, it is crucial to note that though BioGlue is safe and effective in its usual applications, several well-documented adverse effects and added risks call into question the long-term safety of using BioGlue priming to mitigate oozing risk.[5] Perhaps more significantly, the need for the generous application of a potentially harmful substance to the aortic graft, brought about by inherent shortcomings in device design, calls into question the overall safety and suitability of E-Vita Open NEO. This is more striking when one recalls that evidence of improved clinical efficacy of E-Vita Open NEO compared to other, non-oozing grafts such as Thoraflex HP, is both sparse and varied.

4.2.1: Inflammation

The propensity for BioGlue to cause local inflammation, with myriad resulting downstream issues, is widely reported in literature. It has been suggested that polymerised BioGlue may continue to release glutaraldehyde, which then exerts a cytotoxic effect on neighbouring tissue, inducing inflammation, oedema, and possibly necrosis.[5] BioGlue-associated application site inflammation is usually sterile and characterised by the presence of inflammatory mediators with downstream clinical manifestations. In the case of a 65-year-old female who developed pericardial effusion with cardiac tamponade, following the use of BioGlue for ventricular laceration repair, Babin-Ebell et al. noted sterile microbiological findings, but with chronic granulomatous inflammatory infiltrate, likely resulting from a foreign-material reaction to BioGlue.[13] Luk et al. also highlight two cases of DeBakey type I aortic dissection involving BioGlue: islands of inflammatory infiltrate (primarily macrophages, giant cells, and lymphocytes) were identified around areas where BioGlue was applied to aortic tissue.[5] Further, BioGlue was also identified as causing a large, sterile abscess with an inflammatory reaction around the prosthetic aortic valve implanted in a patient with suspected bacterial endocarditis.[5] It is worth highlighting that CryoLife warn against applying thick layers of BioGlue: this is said to slow proteolytic degradation of the product, which may then precipitate a sterile inflammatory response.[7] In addition to localised inflammatory responses, BioGlue has also been associated with impaired aortic growth, nerve injury, and pseudoaneurysm formation.

4.2.2: Effect of BioGlue on surrounding tissues

LeMaire et al. investigated, using a porcine model, the effect of BioGlue on aortic growth. It was found that aortic growth was attenuated in piglets assigned to undergo anastomotic reinforcement of the aorta with BioGlue, and that those piglets also developed 33.9% stenosis of the aortic lumen and adventitial changes reflective of tissue fibrosis ($P = 0.038$ and $P = 0.008$ respectively).[4] LeMaire et al. in 2005 also concluded that BioGlue harmed nerve and cardiac conduction tissue via direct contact. Considering the proximity of the FET prosthesis to the recurrent laryngeal nerve, the risk of causing non-mechanical, irreversible recurrent laryngeal nerve palsy by liberal application of BioGlue must be considered. Mechanical valve obstruction, bypass graft stenosis, pulmonary embolism, and cardiac tamponade are further examples (albeit rare) of complications associated with BioGlue use.[13,14,15]The effect of BioGlue hardening on surrounding tissues is also worthy of consideration. Azadani et al. found BioGlue to exhibit the most stiffness compared to other commercially available alternatives ($P < 0.001$), and though they rightly point out that this may reduce the risk of arterial stretching and eventual pseudoaneurysm formation in vessels strengthened with BioGlue, it could be argued that BioGlue priming of E-Vita Open NEO may stiffen the graft, making reintervention difficult and dangerous.[16] Leone et al. cite reintervention rates for thoracic aortic aneurysms as being as high

as 39.6%, and 23.7% for aortic arch dissection.[17]Considering these high rates of reintervention, is hardening of the graft surface with BioGlue the best long-term option?

4.2.3: Pseudoaneurysm formation

Pseudoaneurysm formation, a particularly dangerous complication, is thought to result from the inflammatory reaction against BioGlue causing altered tissue integrity.[18.19] Suzuki et al suggest that excessive BioGlue use can cause aortic wall necrosis and pseudoaneurysm development, and indeed Luk et al. point out three cases of pseudoaneurysm attributed to BioGlue use in aortic surgery.[1,5] Ngaage et al. note that pseudoaneurysm formation may take up to two years following initial application of BioGlue for type A dissection – this is particularly worrying considering the long-term effects of BioGlue graft priming are unknown.[20]

4.2.4: BioGlue Embolism

The risk of thromboembolism in aortic surgery is omnipresent but is typically surrounding the use of adjunctive cerebral perfusion and surgical manipulation of the diseased aorta. It is important to highlight that BioGlue, despite being broken down by proteolysis after application, still poses a risk of embolism.[21] Carrel et al. suggest that surgical adhesive embolization usually occurs via one of three routes: inadvertent spillage into the true lumen (TL), leakage through a distal re-entry tear into the TL, or leakage through anastomotic needle holes into the TL.[21] The last has been proven by LeMaire et al. in 2005, who further concluded that intramural adhesive particles dislodge and embolise easily.[22] All three routes are real risks when priming E-Vita Open NEO with BioGlue – embolization to the coronary arteries, pulmonary circulation, brain, and limbs have all been reported in literature.[22] Particles of polymerised surgical glue, for example, have been identified in cerebral vessels during post-mortem of a patient who had undergone FET for TAAD but did not show clinical evidence of stroke.[21] LeMaire notes that BioGlue leaks through suture tracts in up to 10% of anastomoses, and that this may occur in spite of proper administration technique.[22]BioGule leaks through prosthetic grafts, such as E-Vita Open NEO, have also been shown to form discrete, round, adhesive particles with a propensity for dislodging and embolising.[22] Gillham and Tousignant described a case of aortic mechanical valve occlusion caused by GRF glue that had entered the aortic TL via aortotomy suture lines.[23] Miller et al. reported extracting large BioGlue 'bullets' from thoracoabdominal aortas in patients that had previously undergone proximal aortic repair, and Mahmood et al. reported a fatal myocardial infarct resulting from embolization of BioGlue to the coronary arteries following proximal aortic repair.[24,25] Crucially, given the significant morbidity associated with major aortocardiac procedures, postoperative stroke and end-organ dysfunction are common complications; these tend not to raise suspicions over adhesive embolization and are usually attributed to factors such as hypothermic circulatory arrest or atherosclerotic thromboembolism.[22] Indeed, because postmortem microscopy studies are not routine in such patients either, it is challenging to accurately ascertain the true extent of adhesive embolic damage, and how this may be augmented by BioGlue priming of the FET prosthesis.[20]

CONCLUSION

Graft oozing is a worrying complication seemingly unique to the E-Vita Open NEO hybrid prosthesis, possibly resulting from its particularly porous graft material. Our experimental data have emphasised the significance of graft oozing in this device and made clear the need for this limitation to be addressed. The recommendation to use BioGlue as a priming agent to prevent oozing is controversial, as BioGlue, though safe and useful in certain surgical applications, is also associated with several major complications.[5] These risks are further amplified considering the amount of BioGlue that would be needed to successfully prime the arch prosthesis, demonstrated by our data as well as by reports published in literature. Bearing the design limitations of E-Vita Open NEO and the added risk of graft oozing in mind, as well as the supplemental risks associated with BioGlue use, it is reasonable to suggest that the device falls short of the providing gold-standard results, especially in comparison to alternative commercially available devices, such as Thoraflex® HP.

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