

A surgeon, a rabbi and a lawyer walk in to an OR... Absorbable haemostatic agents and the dangers of product evolution – clinical, religious and legal implications

Laurence Gluch¹, Nicky Gluch²

1. The Strathfield Breast Centre, The University of Sydney, Australia
2. The University of Sydney, Australia

CASE STUDY

Please cite this paper as: Gluch L, Gluch N. A surgeon, a rabbi and a lawyer walk into an OR... Absorbable haemostatic agents and the dangers of product evolution - clinical, religious and legal implications. AMJ 2018;11(1):18–24. <https://doi.org/10.21767/AMJ.2017.3268>

Corresponding Author:

Dr Laurence Gluch
The Strathfield Breast Centre
The University of Sydney, 3 Everton Road
Strathfield NSW 2135, Australia
Email: lgluch@mail.usyd.edu.au

ABSTRACT

Adjunctive haemostatic agents have been used in surgery for over 70 years. What surgeons may not know is that products intended for similar applications may have very different biological properties and that occasionally product upgrades may introduce a change in the material's behaviour. Many of the agents employed to assist in haemostasis may have a biological (animal) origin. A recent case brought to light the need to recognise the possibility of biological interactions. As consideration into this surgical problem unfolded, religious and legal questions began to arise.

Key Words

Breast reconstruction, haemostatics, adverse effects

Implications for Practice:

1. What is known about this subject?

This case suggests the possibility that some “inert”

haemostatic agents may result in allergic type reactions. It has not previously been reported.

2. What new information is offered in this case study?

The complex biological origin of haemostatic agents and the biological, religious and legal implications of using them.

3. What are the implications for research, policy, or practice?

This article should lead us to carefully review our choice of haemostatic agents.

Background

Breast reconstruction following cancer surgery has a recognised complication rate. Often the first sign that the prosthesis may be infected is the appearance of a red breast. A recent case highlighted the possibility that allergic type reactions, rather than infection, may occasionally result in a red breast. The possibility that this reaction was caused by a haemostatic agent is suggested. It is important to recognise the diverse origins of various haemostatic agents, and how their biological interactions may lead to adverse clinical sequelae. The religious and legal implication of using haemostatic agents in a population of increasing religious diversity is also discussed.

Case Presentation

A 36-year-old patient who three weeks earlier had undergone bilateral nipple-areola sparing mastectomies with subpectoral expander placement presented with increasing erythema of her left breast. Nine years earlier she had undergone a wide excision and axillary dissection for a right breast cancer followed by 3-field radiotherapy to the breast, supraclavicular nodes and internal mammary chain.

Post-operatively there was persistence of a pre-pectoral seroma in the previously untreated (left) side. This was

repeatedly aspirated under ultrasound guidance, and always appeared clear. Close attention was paid to the site of origin of the fluid; it always appeared to be pre-, rather than sub-pectoral (peri-prosthetic). By the end of the third post-operative week a small area of reactive skin erythema was seen lateral to the nipple. A few days later this had become more extensive and concerning in appearance (Figure 1). The pre-pectoral space was again aspirated. No organisms were cultured from the fluid. The patient's white cell count and C-reactive protein (CRP) levels remained normal. The patient was commenced on Flucloxacillin to cover the likeliest organisms implicated in implant infections. Over the course of the next few days the patient monitored her white cell count and CRP, which remained normal. At the next follow up visit the erythema had extended, but maintained a vasculitic, rather than cellulitic appearance (Figure 2). The senior author (LG) had by now considered that the cause of the rash might be an irritant. A 16-gauge cannula was inserted into the space and the cavity space aspirated and washed out with normal saline. The contents of the aspirate showed particulate matter (Figure 3), considered to have arisen from a piece of oxidised cellulose placed into the pre-axillary recess in the upper outer quadrant of the breast pocket to control a small bleeder. (Intraoperatively the patient was administered full heparin DVT prophylaxis given the length of the operation, and the concern regarding perfusion of the skin flaps, especially on the previously irradiated side.) Rapid resolution of the erythema was observed over the next few days.

The senior author has prior experience using an earlier brand of oxidised cellulose, manufactured by the same company, in similar situations. Usually the drain discharge was noted to be darker, often black; however the original brand of oxidised cellulose tended to dissolve within a fortnight. Persistence of oxidised cellulose up to three weeks, as in this case, was considered unusual.

The Surgeon – Haemostatic agents

Implant loss in breast reconstruction surgery is a debilitating complication that leads to increased hospitalisation, adverse psychosocial sequelae, and oftentimes failure to complete reconstruction.¹ Persistence of peri-prosthetic fluid and the presence of skin erythema are often the earliest manifestations of implant infection. Some of the manifestations of the case above led the author to have serious concerns regarding a peri-prosthetic infection. The resolution of the skin erythema after aspiration and irrigation of the pre-pectoral space allayed those concerns.

Adjunctive haemostatic agents have been used for over 70 years.² Oxidised cellulose and porcine gelatine sponge have been in use since the 1940's. From the 1970's bovine collagen and flowable bovine collagen with bovine platelets or flowable bovine gelatine matrix mixed with bovine thrombin have been adopted. Oxidised regenerated cellulose was developed in the 1960's with subsequent product evolution leading to the introduction of newer versions. The cellulose and gelatine preparations possibly activate clotting through contact activation, while the collagen based products act through a dual mechanism of contact activation and platelet aggregation.² The combination of a gelatine matrix and thrombin assists in the stabilisation of the resultant thrombus. Cellulose, being a plant product, is considered inert,³ however the animal origin of the other products means that they contain biological activity with possible sequelae.

The package insert for all three oxidised cellulose brands produced by one manufacturer claims that these three different preparations consist only of oxidised regenerated cellulose. That the texture, appearance and odour of the various products appears so different raises some concerns that perhaps some other agents may be added in the manufacturing of these materials that may not warrant full disclosure. In 1976, with the Medical Device Amendments to the United States Federal Food, Drug and Cosmetic Act, haemostatic agents were no longer classed as drugs, but rather as devices.⁴ It is possible that oversight of adverse drug reactions, and the labelling of such materials may, as a consequence, have become less stringent.

The bovine and porcine origins of the gelatine, collagen and thrombin haemostatic agents may lead to allergies or the development of inhibitory antibodies.⁵⁻⁷ Granulomatous foreign body reactions and excessive fibrotic reactions may lead to catastrophic sequelae, particularly when the agents have been used within the abdominal cavity. Cases of appendicitis,⁸ small bowel obstruction⁹ and caseating peritoneal granulomas¹⁰ have been described.

Reports in the medical literature of adverse effects secondary to the use of haemostatic agents in breast surgery seem to be sparse. A Medline search of *hemostatics (adverse effects)* with linkage to *mastectomy, mammoplasty or surgery, plastic* yielded only one reference.¹¹ A further search revealed a case of a patient who, following an augmentation mammoplasty, experienced a marked allergic wound reaction to the use of 2-octyl cyanoacrylate used for skin closure rather than haemostasis.¹²

The development of breast erythema following prosthesis-based reconstruction is a worrying portent of possible peri-prosthetic infection with considerably high implant loss rates.¹³ Infection rates of up to 35 per cent have been reported in reconstruction cases.¹⁴ The presence of a raised white cell count, a history of previous radiotherapy to the breast or the culture of atypical bacteria (e.g., gram negative rods or methicillin resistant *S. aureus*) are reportedly associated with higher implant loss rates.¹⁵ There is some controversy in the literature as to whether the inclusion of biological matrices, particularly acellular dermal matrix (ADM) around the implant¹⁴⁻¹⁷ may increase the risks of peri-prosthetic infection. Use of ADM has been associated with the phenomenon of “red breast syndrome”,¹⁴ painless blanching erythema, which is not infectious in origin and is self limiting over weeks to months. Breast fluid collections mostly develop in the **pre-pectoral** space,¹⁸ however use of ADM has been reported to increase **peri-prosthetic** fluid volumes, and seroma duration.¹⁷ Strategies which aim to salvage infected breast implants are well covered in the literature^{1,14,15,19} and this paper will not expand on this further.

In the case presented in this paper the patient fortunately retained a normal white cell count, and no growth was isolated from the fluid aspirated. She had also had radiotherapy to the side contralateral to the erythema, and partial areolar necrosis was evident in this, the irradiated side. This reassuringly led to a greater belief that the unfolding erythema was secondary to a reactive, rather than infective cause. That the clinical progress of the erythema, and the dramatic response following lavage of the pre-pectoral space with the subsequent removal of most of the foreign material, leading to a dramatic resolution of the erythema, attests to the allergenicity of the material.

The Rabbi - Biological materials and religious beliefs

A literature search on the biological origins of haemostatic agents revealed a landmark Australian paper in this field. Easterbrook and Maddern,²⁰ recognising that little was published in the Medical Literature regarding the acceptability of porcine and bovine surgical products, reviewed religious written sources and surveyed leaders from the Jewish, Muslim and Hindu communities to gauge community acceptance of these products. The current paper has also reviewed the literature since Easterbrook and Maddern’s article to ascertain broader international opinion. They, and other authors since,^{21,22} suggest that it is part of a surgeon’s duty of care to discuss the possible or intended use of animal derived products as part of informed

consent. Before considering the implications of such a recommendation it would be appropriate to distil the consensus opinions regarding the suitability of animal derived products amongst various religious groups.

Grabenstein presents an excellent exposition of the acceptance of animal products by all of the world’s major religious groups in regards to vaccines.²³ The conclusions from that paper are as valid regarding the acceptability of implantable surgical materials. A cautionary note by that author is that scriptural and canonical texts may not be interpreted uniformly by all practitioners of a particular faith group; their basis for objection may be more social or philosophical rather than theological.

It is well known (certainly in countries with Christian majority populations) that Jehovah’s Witnesses object unwaveringly to blood transfusion.²⁴ This pertains to whole blood transfusions, even auto-transfusion. The use of blood-derived products is allowable, with even fractionated blood components being considered permissible.²³ Jehovah’s Witnesses have no objection to the use of implantable animal derived products.

Jews and Muslims refrain from eating pork, and Hindus refrain from eating beef. Many other Hindus, and many Buddhists practice vegetarianism, their objections being to the killing of any life form.²³ Jewish law permits the suspension of almost all Jewish commandments (laws) to save a life.²³ This means an overarching acceptance of surgical products and devices, irrespective of their biological source, as a necessary means to restore health or function. Muslims share a similar respect for the value of life permitting the use of even porcine products if no alternates are available²⁰ while others allow a more discretionary approach with followers of the religion asked to consult their local leaders for guidance.²⁰ This means that some Muslims will accept the use of all biological materials except those of porcine origin while others believe in avoiding any animal derived products and using alternate materials, even if this may mean a longer time to heal or a greater cost.²¹ The Islamic Institute of Australia has suggested that in extreme circumstances, namely a life-threatening situation, porcine products may be considered.²⁰ Jewish ethical opinion would counter that withholding a product may lead to an as yet unapparent life-threatening situation and therefore such products should be used.^{25,26}

For Hindus total avoidance of the use of bovine (and porcine) derived products may be advocated.^{20,27} However, as Hinduism is considered more a collection of religious

practices rather than a central faith²⁸ observances may vary with some recommending consultation with a religious leader,²⁸ while others propose a total waiving of religious belief in emergency situations.²⁷ Buddhists generally permit the use of biological materials²⁸ unless the animal was specifically killed to derive that product. Seventh Day Adventists, many of whom practice vegetarianism, or if they eat meat, will avoid pork, also permit the use of biological materials.²⁸

Goyal et al. have proposed that professional bodies and religious leaders should come together to form an “Ethical Understanding” to try rationalising usage of these biological products.²² Given the understandably wide variation in different religious viewpoints and practices such a proposal would be unworkable; indeed a common policy can never be forthcoming.²⁹ Thus it appears that the status quo of variability will remain, which creates a predicament. Some of the authors cited above contend that it is a surgeon’s duty to know the possible animal source of a product before using it,²² whereas in reality ignorance as to a product’s origin is the norm.²¹ Before encountering the above case, the subject of this paper, these authors were oblivious to the range of biological materials in general usage, and how similar products may differ so widely in their origin. Simultaneously, Easterbrook and Maddern claim that the “failure to inform patients of what constitutes a product is a violation of Article 9 of the Human Rights Act, which states that “everyone has the right to manifest his religion or belief, in worship, teaching, practice and observance””.²⁰

The Lawyer - Consent and the law

“[T]rue consent to what happens to one’s self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each.”³⁰

Decision making in relation to medical treatment centres around two bases for such decision-making – consent and the concept of best interests.²⁴ Under Australian law consent or refusal is valid if a patient is mentally competent and the decision was made voluntarily.²⁴ Meredith Blake, in an expansive paper outlining religious beliefs and medical treatment (but more particularly pertaining to end of life matters), raises “the notion that ‘informed consent’ brings with it the promise of patient choice, and therefore a full recognition of self-determination in clinical care”... but that...“in reality this is not part of Australian law.”²⁴

The law of consent in recognising the (Judeo-Christian) value of life is structured more around the particular conception of what is harmful and what is good and places less emphasis on concerns of other faiths. As Blake states:

“To this extent it might be argued that the law is, at best, incomplete, or, at worst, discriminatory in its failure to accord any prominence to the link between faith and decisions about health care. However any such conclusion ignores the prescriptive question – should the law on consent be applied so that it can reflect these choices?...”

...Moreover, it is debatable whether the law should condone those decisions, which, although based in religious belief, threaten the very purpose which health care seeks to carry out. If there is one common feature between diverse religions and cultures it is that health care professionals are there to help save lives and improve quality of life through the provision of treatment.”

This raises the question of whether a patient’s wishes should take precedence over a doctor’s choices? In a national survey conducted in the United States of America, Lawrence and Curlin³¹ ascertained that doctors believe patients wishes are important but other considerations are often equally or more important. They demonstrated that a patients’ autonomy does not guide physicians’ decisions as much as idealised, with only a minority of doctors surveyed believing that religious or traditional beliefs should receive the highest weighting.

Blake argues that the law should remain tied to the conception of autonomy but does not lessen the need for broader communication in a religiously diverse community. Evolutionary change in the way communities understand ethical pursuit of healthcare needs to occur before changes in the law need to be considered. A ‘softer’ notion of autonomy, one which is “less individualistic in nature and which is grounded in the interdependence of human beings” needs be realised;²⁴ one that recognises that “interdependency is central to autonomy”.

The Dilemma - Letting Schrödinger’s cat out of the bag

Does this very article pose a dilemma; by raising this topic are we revealing what to date was largely unknown or unmentioned, yet in revealing as much are we creating a situation that can have only one of two possible outcomes?

When considering the Case Presentation from a surgeon’s perspective, the solution seems simple: Medical Device companies should be obliged to label their products

rigorously so as to reduce the risk of allergic and other adverse reactions. When considering the Case from a religious perspective, however, the solution appears to the surgeon's detriment. If patients become aware that biological materials come from a variety of sources, this could lead to greater patient driven requests to refuse use of certain materials in the operating theatre. But can a surgeon always know before hand when he/she may need a biological material and what limitations may be imposed on him/her if certain choices are unavailable?

A scientific paper should deal with facts, at least as best as they can be substantiated, while law, dealing necessarily more with opinion and precedence, must have the scope to evolve as situations and understandings change. Australian Law is principled on Judeo-Christian Law. Of the religions Judaism has one of the most stringent dietary codes, yet has one of the widest acceptances of the principle to "heal", no matter what other principles may be at stake. If it weren't for this convergence with Christian healing principles greater confrontations may have arisen in the past. Australia is a multicultural country. Other religious groups are increasingly represented in the population, and an understanding or empathy for more widely held religious principles is required. A workable policy needs to be applied to avoid needless misunderstanding, or worse, confrontation, where religious ideologies and practices differ.

Perhaps an opinion can be proffered. At this stage it would not be commonplace for surgeons to enquire as to the religious background of patients; this need not change in the short term. However, where a surgeon may surmise a patient's religion he thus becomes knowing of a potential conflict. In situations in which biological devices are to be permanently implanted, e.g., cardiac valves, orthopaedic implants etc. the patient should be appraised that such devices are to be used, and those suitable alternates may not be available. Haemostatic agents, however, differ from other biologically derived devices in that their use, while essential, is often unplanned. Autonomy thus needs to rest in the hands of the surgeon whose duty it is to save a life. The patient is not in the position to make an informed decision; but the surgeon needs to be. This is why haemostatic agents should be better labelled. In line with the religious ideal of 'improving quality of life through treatment', surgeons need to have full information at hand to compare products, select that which they think most suitable and be aware of what and why side effects may arise.

Conclusion

This paper started as a scientific paper, by the end it was more concerned with matters of the Law. It has raised the matter of unintended clinical consequences that may arise from the use of biological material, but has progressed to raise matters of wider import. Secularisation and religious autonomy may both be seeking hegemony, especially in "Western" societies. The need to recognise our shared values, but also our differences, may require skilful juggling and diplomacy. Surgeons have always had to balance their professionalism with their patients' needs and desires. The fact that implantable materials may be contrary to their patients' wishes may be something they now have also to consider.

References

1. Meybodi F, Sedaghat N, French J, et al. Implant salvage in breast reconstruction with severe peri-prosthetic infection. *ANZ J Surg.* 2015;doi:10.1111/ans.13379.
2. Gabay M. Absorbable hemostatic agents. *American Journal of Health-System Pharmacy.* 2006;63(13):1244–1253.
3. Albala DM. Biosurgicals and Hemostasis. http://www.globalroboticsinstitute.com/sites/default/files/protected_files/ToolsforHemostasis.pdf. Accessed 11 January, 2017.
4. Keshavarzi S, MacDougall M, Lulic D, et al. Clinical experience with the surgicel family of absorbable hemostats (oxidized regenerated cellulose) in neurosurgical applications: a review. *Wounds: a compendium of clinical research and practice.* 2013;25(6):160–167.
5. Ortel TL, Charles LA, Keller FG, et al. Topical thrombin and acquired coagulation factor inhibitors: clinical spectrum and laboratory diagnosis. *Am J Hematology.* 1994;45(2):128–135.
6. Spero JA. Bovine thrombin-induced inhibitor of factor V and bleeding risk in postoperative neurosurgical patients. Report of three cases. *J Neurosurgery.* 1993;78(5):817–820.
7. Sarfati MR, Dilorenzo DJ, Kraiss LW, et al. Severe coagulopathy following intraoperative use of topical thrombin. *Annals of Vascular Sur.* 2004;18(3):349–351.
8. Teloken PE, Bowles T, Sparrow S. Appendicitis caused by gelatin-based haemostatic agent. *ANZ J Surg.* 2016;86(11):944–945.
9. Clapp B, Santillan A. Small bowel obstruction after FloSeal use. *JSLs.* 2011;15(3):361–364.
10. Shashoua AR, Gill D, Barajas R, et al. Caseating granulomata caused by hemostatic agent posing as metastatic leiomyosarcoma. *JSLs.* 2009;13(2):226–228.

11. DeLustro F, Smith ST, Sundsmo J, et al. Reaction to injectable collagen: results in animal models and clinical use. *Plast Reconstr Surg*. 1987;79(4):581–594.
12. Perry AW, Sosin M. Severe allergic reaction to Dermabond. *Aesthet Surg J*. 2009;29(4):314–316.
13. Sood S, Elder E, French J. Nipple-sparing mastectomy with implant reconstruction: the Westmead experience. *ANZ J Surg*. 2015;85(5):363–367.
14. Washer LL, Gutowski K. Breast implant infections. *Infect Dis Clin North Am*. 2012;26(1):111–125.
15. Reish RG, Damjanovic B, Austen WG Jr., et al. Infection following implant-based reconstruction in 1952 consecutive breast reconstructions: salvage rates and predictors of success. *Plast Reconstr Surg*. 2013;131(6):1223–1230.
16. Liu AS, Kao HK, Reish RG, et al. Postoperative complications in prosthesis-based breast reconstruction using acellular dermal matrix. *Plast Reconstr Surg*. 2011;127(5):1755–1762.
17. Israeli Ben-Noon H, Farber N, Weissman O, et al. The effect of acellular dermal matrix on drain secretions after immediate prosthetic breast reconstruction. *J Plast Surg Hand Surg*. 2013;47(4):308–312.
18. Moyer KE, Potochny JD. Technique for seroma drainage in implant-based breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2012;65(12):1614–1617.
19. Tong RT, Kohi M, Fidelman N, et al. Clinical outcomes of percutaneous drainage of breast fluid collections after mastectomy with expander-based breast reconstruction. *J Vasc Interv Radiol*. 2013;24(9):1369–1374.
20. Easterbrook C, Maddern G. Porcine and bovine surgical products: Jewish, Muslim, and Hindu perspectives. *Archives of Surgery*. 2008;143(4):366–370.
21. Enoch S, Shaaban H, Dunn KW. Informed consent should be obtained from patients to use products (skin substitutes) and dressings containing biological material. *J Med Ethics*. 2005;31(1):2–6.
22. Goyal D, Goyal A, Brittberg M. Consideration of religious sentiments while selecting a biological product for knee arthroscopy. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(7):1577–1586.
23. Grabenstein JD. What the world's religions teach, applied to vaccines and immune globulins. *Vaccine*. 2013;31(16):2011–2023.
24. Blake M. Religious Beliefs and Medical Treatment: The Challenge to Patient Consent. *Bond Law Review*. 2007;19(1):1–35.
25. Tatz A. Medical Halacha (Law) - Principles of Medical Halacha. <http://www.simpletoremember.com/media/a/principles-of-medical-halacha/>. Accessed 19 February, 2017.
26. Tatz A. Medical Halacha (Law) - One Ventilator, Two Patients. <http://www.simpletoremember.com/media/a/one-ventilator/>. Accessed 19 February, 2017.
27. Eriksson A, Burcharth J, Rosenberg J. Animal derived products may conflict with religious patients' beliefs. *BMC Med Ethics*. 2013;14:48.
28. Jenkins ED, Yip M, Melman L, et al. Informed consent: cultural and religious issues associated with the use of allogeneic and xenogeneic mesh products. *J Am Coll Surg*. 2010;210(4):402–410.
29. Boyd K. Religion, reason, controversies and perspectives in clinical and research ethics. *J Med Ethics*. 2015;41(11):863–864.
30. *Canterbury v Spence*. 464 F 2d 77, 780 (DC cir. 1972).
31. Lawrence RE, Curlin FA. Autonomy, religion and clinical decisions: findings from a national physician survey. *J Med Ethics*. 2009;35(4):214–218.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

PATIENT CONSENT

1. The authors, *Gluch L, Gluch N*, declare that:
2. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
3. All possible steps have been taken to safeguard the identity of the patient(s).
4. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Reactive skin erythema at end 3rd post-operative week



Figure 2: Further extent of skin erythema



Figure 3: Particulate aspirate from left pre-pectoral space

