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

Laurence Gluch¹, Nicky Gluch²

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

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. 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. 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. The combination of a gelatine matrix and thrombin assists in the stabilisation of the resultant thrombus. Gelatine, being a plant product, is considered inert, 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. 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. 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, small bowel obstruction and caseating peritoneal granulomas 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. 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.
The development of breast erythema following prosthesis-based reconstruction is a worrying portent of possible peri-prosthetic infection with considerably high implant loss rates. Infection rates of up to 35 per cent have been reported in reconstruction cases. 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. There is some controversy in the literature as to whether the inclusion of biological matrices, particularly acellular dermal matrix (ADM) around the implant may increase the risks of peri-prosthetic infection. Use of ADM has been associated with the phenomenon of “red breast syndrome”, a 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, however use of ADM has been reported to increase peri-prosthetic fluid volumes, and seroma duration. Strategies which aim to salvage infected breast implants are well covered in the literature 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, 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, 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. 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. 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. 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. Jewish law permits the suspension of almost all Jewish commandments (laws) to save a life. 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 available while others allow a more discretionary approach with followers of the religion asked to consult their local leaders for guidance. 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. The Islamic Institute of Australia has suggested that in extreme circumstances, namely a life-threatening situation, porcine products may be considered. 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. For Hindus total avoidance of the use of bovine (and porcine) derived products may be advocated. However, as Hinduism is considered more a collection of religious beliefs...
practices rather than a central faith, observances may vary with some recommending consultation with a religious leader, while others propose a total waiving of religious belief in emergency situations. Buddhists generally permit the use of biological materials 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.

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. 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. 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, whereas in reality ignorance as to a product’s origin is the norm. 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”.”

The Lawyer - Consent and the law

“True 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.”

Decision making in relation to medical treatment centres around two bases for such decision-making – consent and the concept of best interests. Under Australian law consent or refusal is valid if a patient is mentally competent and the decision was made voluntarily. 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.”

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 Curlin 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; 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
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.

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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