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ORIGINAL ARTICLE

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Carboxy-methyl cellulose hydrogels used to fill breast implants: 15 years of experience

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Abstract Three hundred and eighty patients over a 15-year period who received pre-filled carboxy-methyl cellulose were analyzed retrospectively. Laboratory and surgical experience with these prostheses indicate that there is a role in augmentation mammaplasty and reconstruction for implants containing this nontoxic, viscoelastic, biodegradable filling material.

Keywords Biodegradability · Carboxy-methyl cellulose · Safety · Breast reconstruction · Augmentation mammaplasty · Silicone gel

Introduction

Our experience with breast implantation spans approximately 35 years, during which time several different types of prosthesis have been used (Table 1). Beginning in 1965, the initial implants were of our own design (international patent, 1965); these could be refilled with normal saline. Approximately 420 patients received these devices, but their use was discontinued in 1970 for the following reasons:

1. Failure of the filling valve due to a manufacturing flaw [17].
2. The container was poorly suited to the contents and tended to fold [16].
3. Increased length of surgery.
4. Risk of infection secondary to intraoperative implant handling.

Over the next 14 years (1970–1984), 840 patients had implants pre-filled with silicone gel. However, in 1980, an increasing number of local long-term complications caused by the presence of a foreign body reaction (siliconoma) were noted [4]. This was due to leakage of silicone gel into the pectoral muscle and the perimplant breast parenchyma.

In 1983, after 20 revision operations with varying postoperative results, we decided to study another filling material with cosmetic characteristics similar to silicone gel; it was biodegradable and therefore easily eliminated by the body should implant failure occur [2]. Carboxy-methyl cellulose (CMC) dissolved in normal saline was chosen in 1984 as the filling material for implants used in 380 patients for augmentation and reconstruction.

CMC possesses several properties that make it an ideal implant filling material. It is a cellulose polysaccharide weighing approximately 10,000 Da, is soluble in water or in serum in any ratio, remains stable at temperatures ranging from 10° to 130°C, has a pH ranging from 2–10, is transparent in solution, has a low oncotic pressure, and has osmotic properties that follow van't Hoff thermodynamics. Once in the gel state, this material does not exhibit cross-linking, and the viscosity of the gel therefore largely depends on its concentration. In addition, the viscosity of the gel remains stable over time.

Several pieces of circumstantial evidence support the safety of CMC. First, this material is a natural product of photosynthesis forming the skeleton of all plant life and

Table 1 Author's 30 years of experience in breast augmentation

Types of mammary implants	Patients per year (*n*)			
	1965	1970	1984	1995
Inflated with saline	420	–	–	–
Pre-filled with silicone gel	–	840	–	–
Pre-filled with CMC gel	–	–	380	–
Pre-filled with saline	–	–	–	28

CMC, carboxy-methyl cellulose.

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is therefore ubiquitous. In fact, 80% of the dust inhaled throughout our lives is cellulose. Second, cellulose is the basis of cotton clothing and wound dressings, both of which come into contact with human tissues without causing any adverse tissue response. This is especially true in the latter instance where there is a breakdown of immunologic barriers. Finally, there are no documented toxic properties attributable to CMC.

Objectively, CMC has served as the basis for many medications and materials implanted or instilled into the human body. For instance, cellulose-based suture material has never been shown to cause an untoward tissue reaction. In addition, this material serves as the vehicle for a great number of medications, including eye lubricants [5], plasma expanders [6, 9, 15], and intraperitoneal agents for adhesion prevention. The biodegradability of the hydrogels depends on their method of preparation and on their degree of substitution and polymerization. Unlike some of the nondegradable or poorly degradable hydrogels, CMC is easily broken down into low-energy compounds such as glucose, carbon dioxide, and water.

Material and methods

This study was performed in two phases. The first phase was a laboratory investigation in 1984, the results of which were confirmed by additional testing for European (CE) approval performed between 1995 and 1998. The second phase consisted of a retrospective analysis of 380 clinical cases from between 1984 and 1998.

Laboratory evaluation

Six-month-old rabbits were chosen; they were isolated, and six male and female couples were each put in a cage. Subcutaneous injections of 4% CMC gel in saline were given on the right side of the abdomen. The injections were given in increasing doses from 1 to 10% of the rabbit's body weight. The animals were fed once a day.

After 1 month, the effects of this material on the test animal and its offspring were then analyzed clinically and histologically for 1 year, beginning at 8 days (Table 2). In terms of local effects, reactive edema was noted to develop in the soft tissues surrounding the injection site proportional to the amount of material injected. This resolved spontaneously after a few days depending on the volume instilled. Systemically, no significant reaction was noticed until 200 g CMC was injected, at which point a loss of appetite was noted in the test subjects. At the cellular level, considerable macrophage accumulation was seen during the first month; however this disappeared by the second month and was followed by slight fibrosis. After 6 months, the injection sites were no longer visible, and on biopsy no histological difference could be found between the injected area and neighboring tissue.

The second part of this phase of the rabbit study involved intravenous injection of 4% CMC gel in increasing doses of 1–50 cm^3 into the marginal vein of the right ear. The effect of this material was then evaluated from the time of injection over a period of 1 month. No adverse effects of the injection were noted until a quantity of 50 cc or more was delivered, at which point the animals succumbed, showing the typical signs of a fatal cerebral embolism (Table 3).

In addition to our laboratory studies, Laboratoires LEMI Technopole (Marsillac, France), to which we were advisors, performed an extensive evaluation of this material as required by the French Ministry of Health. The results are summarized in Table 4.

Table 2 Reaction in rabbits and their offspring after subcutaneous injections of 4% CMC gel

Weight of gel injected (g)	Local reaction after 8 days	General reaction after 8 days	Effect on offspring after 1 year
20	None	None	None
50	Slight edema	None	None
100	Edema	None	None
200	Severe edema	Loss of appetite	None

Table 3 Clinical signs in rabbits after intravenous injection of 4% CMC gel

Quantity injected intravenously (cc)	Immediate clinical signs	Clinical signs at 1 month
1	None	None
10	None	None
50 (injection in less than 10 s)	Dead from cerebral embolism (immediate mydriasis	–

Clinical evaluation

Our use of pre-filled CMC gel prostheses began in 1984, and a total of 380 women received implant in our center over a period of 11 years. The indications for use and placement of the prosthesis were the same as for other breast implants. Generally, these were placed behind the pectoral muscle in patients with aplasia (30%) and implanted in the subglandular position if the thickness of breast parenchyma and subcutaneous tissue was adequate (70%). The surgical approach (inframammary, periareolar, or transaxillary) was agreed upon by the patient and the surgeon. The most common one was the transaxillary subglandular approach, because this is simplest and allows good hemostasis to be performed. The reason for surgery was cosmetic in 95% of patients, and in this group two implants were placed in each patient. The remainder of implants were inserted for reconstruction.

Results

A review of the 380 operations performed between 1984 and 1998 revealed 51 implant failures: 3 accidental or perioperative ruptures, 12 early ruptures, and 39 long-term failures. Between 1986 and 1987, there were 12 deflations due to patch detachment as a result of a manufacturing flaw; this occurred 3–6 months after implantation. Detachment of the patch produced rapid leakage of the implant contents into the surrounding soft tissue. As in the laboratory rabbits, the CMC only produced a reactive edema 8 days after rupture. No other clinical signs (such as pain, redness, or increased temperature) occurred. There were no long-term effects of the local effusion of hydrogels (Table 5). In each case, however, the patient returned to ask whether a mistake had been made in selecting the proper-sized implant. We found that reactive edema is pathognomonic for implant leakage or rupture and is a clear indication for prosthesis replacement. The latter is performed as soon as possible after rupture (average, 8 days). None of the patients developed an infection of

Table 4 Results of a study of CMC gel

Cytotoxicity	Acute toxicity	Skin irritation	Sensitization	Hemocompatibility	Mutagenicity
None	Negative	Negative	None	Good	None

Table 5 Ruptures, leaks, and revision surgery

Year	Accidental or sudden perioperative rupture (*n*)	Long-term leak and revision surgery (*n*)	Associated clinical signs
1990	1	7	Usually none
1995	2	17	Usually none
1998	0	15	Occasionally painful sensation on mobilizing the implant, more obvious if the capsule had retracted

the operative site either at the time of the initial surgery or perioperatively at the time of replacement.

The replacement procedure was easily performed under local anesthesia and did not require the formation of a new pocket or adjustment of the existing pocket. In fact, we have never experienced difficulties when replacing these implants either technically or from the point of view of patient acceptance. All patients were clearly informed preoperatively about the risk of implant leakage or rupture and the need for a second operation should this occur. All implants were replaced shortly after the diagnosis of rupture was made, the average time being 8 days. Preparing the pocket by irrigating it with normal saline or hydrogen peroxide was sufficient to cleanse the cavity prior to inserting the new prosthesis.

Tissue specimens were obtained at the time of revision and sent for histological examination. The latter showed only a relatively mild inflammatory macrophage reaction, indicating rapid degradation and elimination of the CMC.

Two patients returned 5 years after the initial surgery with progressive deflation on one side. Unlike the previous group of patients, in which the diagnosis was made at an early stage, surgical revision of the implant pocket was necessary because of tissue contraction around the empty implant shell. The capsule was entirely normal in thickness, and no inflammation or foreign body reaction was found. Ruptures (apart from the manufacturing defect in 1986) are summarized in Table 5.

Of the 380 patients, 13 experienced capsular contracture. Three patients developed stage III contracture within 3–4 months of the initial surgery. The remaining ten developed stage III and IV capsular contracture 4–5 years after surgery. All of these implants were replaced after increasing the size of the existing implant pocket. Although the numbers are small, the position of the implant in relation to the pectoral muscle did not seem to be significant in causing capsular contracture.

Discussion

Regarding the failure rate of CMC implants, our results are not significantly different from other published findings, which report a deflation rate of approximately 4–6% over 10 years [1, 3, 4, 17]. The considerable technical progress in the fabrication of these implants, particularly with autologous soldering of the monobloc implant patches, has already resulted in better long-term results, although it is too early for these to be published.

It is quite remarkable that, in contrast to the silicone gels [7, 8], the mechanical properties of the implant shell are not affected by the aqueous CMC solution [3]. In addition, one of the principle advantages of CMC is its biodegradability. If the contents of a breast implant are not degradable, as in the case of silicone gel, or are poorly degradable, such as fatty acids, then the diagnosis is made at a late stage. This in turn results in local mesenchymal retraction reactions and/or the development of granulomas.

After considerable clinical and laboratory experience, we believe that the retractile fibroblast reaction is not related to the nature of the implant. This reaction, which we call the "fibrous capsule," has different causes depending on the time when it appears [10, 11, 12, 13, 14].

Short-term capsules, i.e., occurring after between 2 and 6 months, have two causes: (1) inadequate development of the surgical cavity into which the implant is placed and (2) the formation of postoperative hematoma, even if it is very small. This is a so-called lenticular hematoma and is the result of phagocytosis of fibrin degradation products. This always becomes fibrous and retractile, and calcium is occasionally deposited. It is for this reason that patients should be instructed to limit their activities for 4–5 days following surgery.

There are also two causes for long-term capsule formation, i.e., after 5 years. First, the transudate (bleeding) of nondegradable implant filling material is phagocytized, and this may or may not result in the formation of inflammatory granulomas [17, 18, 19]. This phenomenon is not totally understood, but it involves activation of complement and cytokines. It is probably programmed by these centers because of its timing. It begins as an immune reaction, which recedes if the foreign body is biocompatible. If not, a capsule of varying thickness is formed. Second, capsule formation is a normal physiologic response of all mesenchymal tissue immediately

surrounding a chemically stable foreign body to minimize the surface to volume ratio between itself and the implant.

Conclusion

After more than 35 years of experience with various type of breast implants, it is considered essential to have the greatest possible reliability of the implant shell and its filling material. Given the many local complications due to leakage of silicone gel, we now use implants with an alternative filling product, i.e., CMC. After more than 15 years of clinical use, this material represents a considerable advance in prosthesis reliability and patient safety.

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EDITORIAL COMMENT

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Carboxy-methyl cellulose hydrogels used to fill breast implants: a 15-year experience

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Since this paper was sent for publication, the British Medical Devices Agency (MDA) have decided to ban two "hydrogel" prostheses: the PIP hydrogel with hydroxy-methyl cellulose and the NovaGold prosthesis with polyvinyl pyrroliodone as a filler. They have advised health authorities, NHS trusts, and primary care trusts in the United Kingdom not to implant the implants, to identify and isolate all stocks of these implants and return them to the suppliers, and also to report any adverse incidence concerning the implanted devices to the MDA.

It is of interest to note that carboxy-methyl cellulose is a very nontoxic substance because it is also has been used in the food industry for more than 50 years, as well as in various medications and in subcutaneous implanted long-delivery medicine systems. In addition to this, the French MDA (G-med) recently accepted that "New Fill" can be used to correct wrinkles. This consists of polylactic acid crystals with a hydrogel carmellose. Dow-Corning in 1992 [1], 1993 [2], and 1994 [3] compared the toxicity of silicone gel with carboxy-methyl cellulose and considered this to be a very innocuous material when this comparison with silicone was made. Therefore it certainly seems as though the carboxy-methyl cellulose of Arion could be one of the safest implant materials available, but of course further investigation is required.

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