Biocompatibility Assessment of Synthetic Sling Materials for Female Stress Urinary Incontinence

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Purpose: We evaluated the performance and complications of currently available synthetic sling materials with a focus on in vitro and in vivo biocompatibility, and acceptance in the human body.

Materials and Methods: We reviewed the MEDLINE® database for relevant literature pertaining to various synthetic sling materials. The Food and Drug Administration regulations regarding the regulation and biocompatibility testing of synthetic meshes were also reviewed.

Results: Many synthetic meshes used for sling construction were introduced before rigorous Food and Drug Administration regulations were passed and, thus, some became associated with unique complications. Most meshes used in pubovaginal and mid urethral sling surgery are associated with high short-term success rates and relatively few intraoperative complications. Despite modifications and additives, slings constructed from polytetrafluoroethylene and polyethylene are poorly accepted by the human body. Flexible, macroporous, polypropylene meshes appear to integrate more completely with human tissue than other synthetic materials. However, multifilament and nonknitted polypropylene slings may integrate poorly.

Conclusions: The composition, weave and pore size of each material are unique. These properties are responsible for the strength and durability of the material, as well as the ultimate acceptance and incorporation in the human body. Each material should be individually evaluated and patients should be counseled appropriately before implantation.

Key Words: suburethral slings, urinary incontinence, prostheses and implants

Although the suburethral sling is rapidly approaching its centennial, the routine surgical use of synthetic materials is a relatively novel practice. While various autologous tissues have been routinely used since 1907, synthetic materials for sling construction were not used until the 1950s, and did not become widely accepted until 30 years later. In the 21st century the durable results of the polypropylene mid urethral sling have solidified the role of synthetic materials as suitable alternatives for autologous fascia.

However, if the entire experience with synthetic materials in surgery is considered, it is only natural to approach their use with some caution. While all of these materials are associated with a host inflammatory response, some may incite a significant cascade that increases the potential for rejection and erosion. Conversely, some materials may also be altered or broken down by the body and lose efficacy. The challenge in identifying the ideal sling material may be further confounded by several host related factors, such as a hypoestrogenic state, radiation exposure and previous vaginal or retroperitoneal surgery. We describe the process of regulating and testing sling materials before marketing, identify the unique properties of each synthetic material available for sling construction using in vitro and in vivo data, and draw conclusions regarding the safety of each material as a sling.

FDA MEDICAL DEVICE REGULATION

A discussion of polymeric sling materials would be incomplete without mentioning medical device regulation, which has a significant role in determining which products are introduced on the market. When the FDA passed the Federal Food, Drug, and Cosmetic Act in 1938, medical devices were typically simple instruments in which defects could be easily identified. Since that time the complexity of medical devices has increased in tandem with the number of devices on the market. The Act initially gave the FDA limited power over medical devices, charging the group with removing preexisting adulterated or misbranded devices from the market. However, the FDA was not granted the authority to review new medical devices before being introduced on the market. Significant changes to the Act were prompted by the Cooper Committee report in 1970, which determined that medical devices contributed to more than 700 deaths and 10,000 injuries during a 10-year period. The majority of these devices were pacemakers, heart valves and intrauterine devices.

The Medical Device Amendments of 1976 were passed after it was concluded that the FDA lacked sufficient authority to adequately oversee public health with respect to medical devices. Among other objectives the Medical Device

Submitted for publication October 4, 2006.

* Financial interest and/or other relationship with Novartis.

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DOI:10.1016/j.juro.2007.05.123

Amendments of 1976 separated all medical devices into pre-amendment and post-amendment devices. Pre-amendment devices (on the market before May 28, 1976) were grandfathered for premarket review and served as predicate devices for post-amendment devices. Post-amendment devices (introduced after May 28, 1976) are required to undergo premarket review. If a manufacturer wishes to market and receive clearance for the same type of device as one that was grandfathered, the manufacturer must submit a 510(k) premarket notification submission demonstrating substantial equivalence. If a new device is deemed substantially equivalent to a pre-amendment device, it may be marketed immediately and is regulated in the same regulatory class as the predicate device.

The Medical Device Amendments of 1976 also required the FDA to classify all devices into 1 of 3 regulatory classes based on the degree of regulation necessary to provide reasonable assurance of device safety and effectiveness. Sling materials are included in the surgical mesh category and are assigned to Class II (Regulation Number 878.3300). Class II devices are subject to general controls and special controls. General controls include prohibition against misbranding and adulteration, premarket notification 510(k) requirements, good manufacturing practices, adverse event reporting, and repair, replacement and refund. Special controls include performance standards, voluntary standards, guidance documents, post-market surveillance, patient registries, and other actions the agency deems necessary to provide reasonable assurance of safety and effectiveness.

The regulation of medical devices is not a flawless process and continues to evolve. For example, before 1990 the FDA did not generally require human clinical trials to determine substantial equivalence. However, with the Safe Medical Devices Act amendments in 1990 the FDA was granted the authority to require the submission of performance data, including data from clinical trials, to make a substantial equivalence determination. Furthermore, the formal definition of substantial equivalence was only established in the 1990 amendments. Thus, a process that allowed post-1976 devices judged substantially equivalent to pre-1976 devices to serve as predicates made it even easier for manufacturers to market their products and avoid the premarket approval process. Because the premarket approval process is often time-consuming and expensive, there appears to be a significant advantage to a manufacturer to claim the device as substantially equivalent to a predicate device. As previously stated, if found substantially equivalent, the new device is placed in the predicate class and can be marketed immediately. Even today the relationship among safety, effectiveness and intricate market forces remains tenuous.

BIOCOMPATIBILITY

Biocompatibility has been defined as "the ability of a material to perform with an appropriate host response in a specific situation."[1] Thus, for a material to perform a specified role in a human body there should be a symbiotic relationship of acceptance between host and material. For a material to perform best it needs to be integrated properly into tissue, generate an appropriate inflammatory response and maintain mechanical integrity (hold shape). These 2 qualities are discussed along with additional and host related factors that contribute to biocompatibility.

Inflammatory Response to Foreign Material Implantation

To understand abnormal integration of a synthetic mesh it is important to first understand the normal host response to mesh implantation. Inflammation may arise in response to the trauma of surgery as well as the intrusion of a foreign body. The first 24 hours after surgery are characterized by noncellular and cellular responses. The initial noncellular inflammatory event is local vasodilatation followed by increased permeability of the vascular endothelium and edema. This event is accompanied by activation of the complement cascade in which the intermediaries and end products not only directly mediate membrane damage, but also produce cellular necrosis and perpetuate inflammation. The cellular response to insult also occurs soon after the implantation of foreign material. Neutrophils, the earliest cells to migrate through endothelial rents, begin phagocytosis, the engulfing and degradation of foreign material by lysozymes and phagosomes. In addition, collagen deposition begins almost immediately after injury. Type III collagen is the main collagen secreted by immature fibroblasts and results in greater elasticity but diminished strength.

Once the neutrophil response begins to ebb, circulating monocytes enter the tissue and become macrophages, continuing phagocytosis. In addition, macrophages release a number of biochemical factors that can mediate the activity of other cells. These factors include lymphocytes, fibroblasts, osteoblasts, osteoclasts and foreign body giant cells. By fusing into a giant cell, activated macrophages can phagocytize larger particles. Because they have a relatively short life span (days), the presence of foreign body giant cells long after implantation suggests a chronic foreign body reaction. After a successful response to an inflammatory challenge, tissue remodeling begins. Dead cells are phagocytized and removed while granulation and neovascularization take place. Newly synthesized Type III collagen and mucopolysaccharides contribute to scar formation, creating a scaffold for cellular reconstruction of the damaged area. After 2 weeks Type III collagen comprises the bulk of the scar. However, this collagen will account for less than 10% of the final tensile strength of the wound.

Scar maturation marks the end of inflammation, and the degree of scarring and capsule formation depends on the degree of original injury, the amount of subsequent cell death and the location of the injury. Replacement of Type III collagen with a stronger, less elastic Type I collagen allows the wound to regain some tensile strength. The result is a dense, fibrous tissue. It should be noted that the aforementioned inflammatory cascade is nonspecific. Thus, the actions of neutrophils and macrophages are universal, and are only slightly affected by the structure and chemical composition of the foreign material.

There also exists a specific or immune response responsible for protecting the body against a specific microorganism or foreign material. The response to foreign materials is determined by the mechanisms of humoral response (production of freely circulating antibodies mediated by B cells) and cell mediated response (T cell). The immune system is constructed to ignore all aspects of self and respond to foreign tissue with an inflammatory response called rejection. Most importantly the immune system adapts by developing a specific memory for particular foreign materials. The result of this memory is undesirable when it results in an