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Polymeric materials for embolic and chemoembolic applications

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ABSTRACT

Percutaneous transcatheter embolization procedures involve the selective occlusion of blood vessels. Occlusive agents, referred to as embolics, vary in material characteristics including chemical composition, mechanical properties, and the ability to concurrently deliver drugs. Commercially available polymeric embolics range from gelatin foam to synthetic polymers such as poly(vinyl alcohol). Current systems under investigation include tunable, bioresorbable microspheres composed of chitosan or poly(ethylene glycol) derivatives, *in situ* gelling liquid embolics with improved safety profiles, and radiopaque embolics that are trackable *in vivo*. This article reviews commercially available materials used for embolization as well as polymeric materials that are under investigation.
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1. Introduction

1.1. Embolotherapy

The concept of embolization, *i.e.*, deliberate blocking of blood vessels, dates back to the early 1900s. Robert Dawbarn presented "the starvation plan" to treat malignant growths in 1904, discussing how physically stopping blood flow to a tumor via ligation of vessels leads to shrinkage and pain relief for the patient [1]. Attempts to use materials to create a physical obstruction to blood flow dates to the early 1930s by Hamby and Gardener who surgically treated carotid-cavernous fistulas using muscle fragments [2]. Percutaneous embolization as a medical procedure was made possible by the early 1960s technological development of the fluoroscope, providing the ability to perform an angiogram by viewing X-rays in real-time. Charles Dotter, considered the "Father of Interventional Radiology", performed the first interventional angiographic procedure in 1964 and was eventually nominated for the Nobel Prize in medicine in 1978. He invented an automated X-ray Roll-Film magazine capable of capturing images every 2 s, as well as various catheters and the J tipped guidewire [3,4]. Later, he introduced the concept of percutaneous transluminal angioplasty and the beginnings of diagnostic coronary angiography. Building off these initial developments, interventional radiology soon advanced to treatment of acute gastrointestinal bleeding, occlusion of arteriovenous malformations and fistulas, to more recent advances in interventional oncology, allowing for chemoembolization of highly vascular tumors such as hepatocellular carcinoma.

The earliest embolizations made use of autologous clots, muscle fragments, or stainless steel pellets. By the 1970s, clinical applications began to drive the development of new materials. Gelatin sponges, first developed as hemostatic materials for open surgery, soon transitioned to use as endovascular embolic agents as a response to failures of muscle fragment embolization. Thomas Speakman reported first use of "mashed" gelatin pieces mixed with saline to a consistency of "good porridge" injected into the internal carotid artery to occlude a carotid-cavernous fistula [5]. The occlusion was successful, eliminating signs and symptoms of the fistula without loss of vision or serious complications in the patient post-operatively.

Embolic materials are classified broadly into mechanical embolic agents or flow-directed embolic agents [2]. Mechanical agents such as metal coils and plugs used to treat focal vascular abnormalities are not within the scope of this review. Flow-directed agents can treat diffuse vascular abnormalities and include particulates, polymers, or *in-situ* gelling biomaterials delivered via catheters positioned within a target's vascular supply. These materials are subcategorized into permanent or temporary. From a clinical standpoint, the therapeutic goal and intended long-term outcome dictate the choice of materials. Questions typically asked include: "Why is embolization necessary?" and "What lies downstream of the intended target?" If embolization is required for obstruction of a hemorrhaging vessel, a temporary, fast acting embolic is required. A vascular malformation, however, often requires a more permanent

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material and more precise administration. Polymers have been successfully designed for a variety of biomedical applications, including as embolic agents [6]. The ability to tailor the polymer structure–function relationship for a defined need provides a unique materials platform. Both natural and synthetic polymers have been used to develop flow-directed embolics [7].

Gelatin sponge made from purified porcine skin is the first example of a successful naturally derived polymer commonly used as a temporary occlusive material [7,8]. The sponge comes in the form of dry sheets that are manually cut into small sections, then mixed with saline and contrast dye just prior to injection. This material provides a fast, low-cost, transient embolic that is used in multiple clinical applications. However, a severe drawback of this agent is lack of precision in delivery, and unpredictable levels of embolization and recanalization [7]. In response, calibrated microspheres (MSs) have been designed using poly(vinyl alcohol) and derivatives to provide improved control [9]. Although with these MSs the level and location of occlusion is highly predictable, they are not degradable and result in permanent vessel occlusion. To address these concerns, degradable materials composed of chitosan derivatives, for example, are being designed for synthesis of microspheres with predictable degradation rates [10]. More recently, biodegradable recombinant silk-elastinlike block copolymers have been used as a liquid embolic [11]. This review highlights these and a series of other embolic materials, first exploring clinical applications followed by material details including physical and mechanical properties, advantages, and disadvantages followed by a discussion of future directions in this field. The article discusses both commercially available agents as well as materials under development.

1.2. Clinical applications

1.2.1. Vascular malformations and hypervascular tumors

Vascular malformations are often congenital anomalies arising from dysplastic vascular channels. They are characterized by a tangle of thin walled vessels whose abnormal characteristics eventually lead to clinical symptoms requiring treatment. Symptoms vary depending on the category of malformation and location in the body and are classified as either slow-flow or fast-flow [2,12,13]. Slow-flow vascular malformations consist of capillary, venous, or lymphatic vessels. Symptoms range from externally visible port-wine staining of the skin to painful cyst-like formations. Fast-flow arteriovenous malformations (AVMs) consist of an arteriovenous shunt bypassing the capillary bed [14] resulting in high flow into the venous system. AVMs within the central nervous system may be particularly dangerous and require treatment to prevent risk of hemorrhage, stroke, neurological deficit, or seizure. Cerebrovascular AVMs are graded by the Spetzler-Martin scale that classifies malformations according to size, location relative to functionally eloquent cortex, and type of venous drainage [15]. Microsurgery for low grade AVMs can provide an immediate cure with a relatively low risk of complications, but remains an invasive procedure. Embolization therapy can be used as a sole treatment method or in combination with surgery or radiotherapy to eliminate or stabilize an AVM, decreasing the risk for hemorrhage [16]. Embolic microspheres are approved for the treatment of AVMs. More recently, liquid embolics, particularly non-adhesive ethylene vinyl alcohol (EVOH) or Onyx®, has been investigated as an improved option [17].

Hypervascular tumors are characterized by tumor induced abnormal vasculature consisting of increased numbers of blood vessels feeding into the tumor. The higher blood flow increases the risk of bleeding during surgical resection. Examples of hypervascular tumors include: head and neck tumors like meningiomas and paragangliomas, hepatocellular and colorectal carcinomas, and subsequent metastases. Embolotherapy is often used to block blood flow to the tumor either as a neoadjuvant method prior to surgery or as a palliative measure if the tumor is inoperable. This treatment not only decreases the risk of bleeding, but also may lead to shrinkage of the tumor thus improving surgical outcome, quality of life, or both. For hypervascular tumors that are operable, neoadjuvant embolization makes use of microspheres, gelatin sponges, liquid embolics or a combination, depending on the clinician or institutional policy. In the past, the primary goal had been solely to block the blood supply of the tumor. In the case of hepatocellular carcinoma (HCC), endovascular therapy has transitioned into a primary treatment involving the co-delivery of chemotherapeutics and embolics. Liver HCC lesions are unique in that they draw blood from branches off of the hepatic artery while the healthy liver parenchyma primarily receives blood supply from the portal system, allowing embolization of the tumor while preserving the surrounding hepatic tissue [18].

1.2.1.1. Transarterial embolization and chemoembolization. Transarterial embolization (TAE) will be explained using treatment of a hepatic tumor as an example. The procedure begins with accessing the arterial system via the femoral artery, using Seldinger technique. Once stable access is established, a guidewire and catheter system is maneuvered to the target location under angiographic guidance. A diagnostic angiogram is performed to identify the vascular supply to the tumor along with any potential anatomic variants [19]. After diagnostic angiography, a vessel is selected for embolization [20]. The catheter is used to access the target vessel, and location is confirmed by injection of contrast. The catheter is then used to deliver the selected embolic. The primary procedural endpoint is angiographic evidence of stasis [21]. Classically, the term TAE in reference to HCC treatment refers to bland embolization where the goal is to induce ischemic necrosis in the tumor. The embolic agents used to achieve this clinical outcome are highly variable. If a temporary occlusion is desired, gelatin sponge is used. If permanent occlusion is intended, poly(vinyl alcohol) or trisacryl gelatin particles are used. However, clinical data over the past few decades has confirmed bland embolization does not provide the best possible outcome [18,22]. Since TAE, chemoembolization was developed to improve patient morbidity and mortality. It is a procedure similar to TAE, but with the addition of localized delivery of chemotherapeutics via the same catheter, termed transarterial chemoembolization (TACE).

TACE can be divided into conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE). Conventional TACE involves sequential delivery of a mixture of chemotherapeutics and ethiodized oil into the tumor vasculature followed by an embolic, whereas the newer DEB-TACE uses a single delivery system of drug loadable microspheres, which both occlude the selected vessels and provide controlled drug release [23]. A series of clinical studies in the past decade have shown benefits of DEB-TACE over cTACE. The PRECISION V study, a multicenter randomized trial comparing the short-term outcomes of DEB-TACE and cTACE, demonstrated that DEB-TACE was associated with improved tolerability, with significant reduction in liver toxicity and chemotherapeutic related side effects [24]. The PRECISION ITALIA study randomized patients to cTACE or DEB-TACE, and required a post-TACE follow-up for at least 2 years or until death. This study failed to establish a significant difference between the two groups in terms of overall survival, but did show significantly lower post-procedural pain in the DEB-TACE group [25]. The DEB-TACE group also showed improved objective response, defined as complete or partial response following the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [26].

Finally, the DEB-TACE process provides several more benefits to the clinician and the patient. Handling chemotherapeutics loaded on beads is less complex, and does not require use of ethiodol, which can dissolve certain types of plastic [27]. Lower pain and systemic toxicity post chemoembolization are important benefits to the patient. Some of the current drawbacks of the available DEBs include permanent occlusion, limited selection of drugs that can be loaded onto the beads, and inability to track bead distribution *in vivo*. Development of degradable microspheres may expand treatment options, allowing treatment of organs and tumors that do not have dual blood supplies. New materials that may load more than one drug type will allow for more personalized medicine and combinational chemotherapy.

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