Clinical Applications of Liquid Embolic Agents

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Endovascular embolization (EE) has been used for the treatment of blood vessel abnormalities, including aneurysms, arteriovenous malformations (AVMs), tumors, etc. The aim of this process is to occlude the affected vessel using biocompatible embolic agents. Liquid embolic agents are usually injectable and delivered into the vascular malformation sites using a catheter guided by X-ray imaging (i.e., angiography). After injection, the liquid embolic agent transforms into a solid implant in situ based on a variety of mechanisms, including polymerization, precipitation, and cross-linking, through ionic or thermal process.

Keywords: liquid embolic agents ; embolization ; Clinical Application

1. Introduction

Endovascular embolization (EE) is a minimally invasive surgical procedure for the treatment of blood vessel abnormalities in various regions of the body. Endovascular treatment decreases hospitalization time and speeds up recovery as compared to open surgery [1]. EE can be used as a sole form of treatment or combined with a presurgical procedure targeted at augmenting blood flow, structure, or pathology. This allows a safer and more effective surgical treatment. EE is performed for the treatment of clinical conditions including aneurysms, arteriovenous malformations (AVMs), tumors, etc. The therapeutic goal of endovascular embolization is the complete occlusion of the affected vessel, reduction of blood flow, and the reduction of the neurovascular disease-related risks and symptoms utilizing an injected or positioned material [2]. Therefore, the safety and effectiveness, biocompatibility, biodegradability, and biomechanical properties of the embolic agents utilized, and optimizing technical aspects of the embolization procedures, are crucial [3]. High selectivity and accuracy, as well as avoidance of undesired events, including vessel perforation, embolization of normal vessels, and reflux, are necessary to perform effective EE procedures. During embolization, embolic substances, including metal coils, tiny spheres, chemicals, and glue, are used to eliminate the vessel or to obstruct blood flow.

Liquid embolic agents are usually injectable and delivered into the vascular malformation sites using a catheter guided by X-ray imaging (i.e., angiography). After the injection, the liquid embolic agents transform into a solid implant in situ, based on a variety of mechanisms, including polymerization, precipitation, and cross-linking, through ionic or thermal processes [3]. The biomaterial characteristics of the liquid embolic agents, including viscosity, solidification time, etc., play an important role in the whole embolization process, starting with the catheter access (diameter: 0.2–3.0 mm, length: up to 200 cm) to the occlusion of the target site by thrombosis or direct obstruction of the lesion [3]. Visibility is a critical safe delivery aspect of liquid embolic agents at the target site and can be achieved by adding several radiopaque additives or using different radiopaque solvents [3].

Embolic materials are classified into solid embolic agents or liquid embolic agents. Solid embolic agents include metal coils and plugs, which are mostly used for the treatment of focal vascular abnormalities [4]. Liquid embolic agents include particulates, polymers, or in situ gelling biomaterials, which are used for the treatment of diffuse vascular abnormalities and are usually deliverable via catheters [4]. Liquid embolic agents can be classified as permanent or temporary. Temporary embolic agents are fast-acting and used for occluding a hemorrhaging vessel, whereas permanent embolic agents are long-lasting and used for the treatment of complex vascular malformation [4].

2. Clinical Applications of Liquid Embolic Agents

2.1. High-Flow Vascular Malformations

High-flow vascular malformations occur when blood flows from a feeding artery directly to a draining vein, bypassing the capillary bed [5]. Because of their high flow, these vascular malformations cause significant rerouting or shunting of blood flow away from surrounding tissue. The two main types of high-flow vascular malformations are known as arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs) [5]. AVMs are composed of abnormal arteries and veins, with

blood shunting occurring through a central collection of dysmorphic vessels (i.e., the nidus) [5]. In an AVF, blood shunting occurs through a single arterialized vein instead of a nidus and is more commonly seen in the central nervous system [6]. The absence of capillaries results in high-pressure blood flow into veins, causing them to widen and often leads to rupture of the vessel. AVMs should be treated quickly to prevent risk of hemorrhage, stroke, heart-attack, neurological deficit, or seizure [4][7]. Cerebral AVMs may cause morbidity and neurological deficit and present a risk of hemorrhaging [8]. Both types of vascular malformations present similar challenges in treatment [5][9], often requiring several embolization procedures (e.g., transarterial embolization, transvenous embolization, or direct puncture embolization), sometimes combined with surgery as the primary treatment option [10].

The goal of endovascular embolization of AVMs is the closure of the whole nidus without occluding other surrounding normal and important vessels [2][11]. Although surgical resection is recommended for the management of AVMs, pre-surgical embolization aims to ease surgical removal, decrease surgery complications, and reduce blood loss during surgery [2][11]. Successful penetration into the nidus and draining vein requires the microcatheter to be positioned less than 1 cm from the nidus, which often cannot be achieved [12]. In such cases, occlusion of the arterial supply is sufficient if the AVM is surgically accessible for subsequent resection [9][11][13]. Incomplete resection or embolization may lead to further angiogenesis, which could increase the angioarchitecture complexity, thus making its subsequent treatment more challenging [10]. For example, angiogenesis may manifest as the creation of new feeders that may be too narrow to allow microcatheter access in subsequent treatment [10].

AVFs remain challenging when embolization is not accompanied by resection in that their high-flow nature may cause embolic materials to migrate into the distal draining veins, potentially resulting in unintentional pulmonary embolization [9] [10]. Similarly, the reflux of liquid embolics into the distal venous drainage or proximal arteries during embolization is often difficult to control and should be prevented. Surgical resection is necessary if venous drainage is observed [10][14]. Reports of successful AVF treatments by endovascular embolization include dural, brain, and scalp arteriovenous fistulas. Dural arteriovenous fistulas (dAVFs) within the dura mater of the brain represent 10–15% of all intracranial AVMs [13][15]. They may present disabling symptoms, and hemorrhage occurs in about 65% of patients [15]. Congenital brain AVFs account for 1.6–4.7% of all brain AVMs and are characterized by the absence of a nidus and their high-flow nature [9]. Although they can be asymptomatic, they can also produce seizures, hemorrhage, and increased and intracranial pressure, among other symptoms that make treatment necessary [8][9]. The large draining vein can interfere with the exposure of the fistula, making surgery challenging and not ideal [9]. Endovascular management facilitates localization of the lesion and enables access to deep and/or critical areas [9]. The heterogeneous angioarchitecture and non-uniform structure of scalp AVFs makes them challenging to treat [10]. Their high-flow shunting can lead to blood loss if the fistula is punctured during resection, for which endovascular management is generally recommended [10].

2.2. Hypervascular Tumors

Hypervascular tumors consist of abnormally large numbers of blood vessels feeding into or contained within the tumor [4]. These tumors are commonly found in the head and neck. Examples include meningiomas, paragangliomas, and hepatocellular and colorectal carcinoma metastases [4]. High-grade gliomas, such as glioblastoma multiforme, may also have significant hypervascular composition. The higher blood flow in the blood vessels increases the risk of bleeding that may create a difficult surgical resection. Presurgical endovascular embolization of hypervascular tumors has proven to mitigate blood loss, operating time, and infection rates from surgical resection [16][17], and may decrease surgical morbidity and mortality [18]. The cost may be high for preoperative embolization of hypervascular tumors due to the large volume required for complete devascularization [16]. However, the advantages of preoperative embolization, in addition to the low complication rate, have increased its preference [16]. For example, anterior skull-based meningiomas fed by the ophthalmic artery may benefit from embolization by reducing the risk of visual impairment [18]. Usually, devascularization is performed using polyvinyl alcohol (PVA) microparticles [17]. When the feeders to the metastatic region also supply the anterior spinal artery, e.g., spinal hypervascular tumors, there is a risk that microparticles will migrate, posing a high risk of neurological complication [17]. When the vessels are small and tortuous, they may not be accessible by micro-catheterization [17]. In such cases, if surgically accessible, direct puncture of the lesion is recommended to administer microparticles or liquid embolic agents [17]. Alternatively, injection of Onyx, a widely used liquid embolic agent, by an endovascular route or by direct puncture has been used to successfully devascularize hypervascular tumors while providing a low risk of uncontrolled migration [17].

2.3. Aneurysms

Aneurysms are dilatations or bulges caused in weakened vessel walls, which can rupture and cause internal bleeding if the tension on the weakened wall increases [4]. Aneurysms can occur throughout the body, but are more common in the

brain, aorta, renal artery, legs, spleen, and AVMs. It is estimated that 6.7 million people in the United States have one or more unruptured brain aneurysms each year, 10% of which need treatment [19]. About 30,000 people in the U.S. suffer an aneurysm rupture each year, which can result in death in 50% of cases, or permanent neurological deficit in 66% of those who survive [19]. The objective of treating aneurysms is their complete and permanent occlusion [20]. Ideally, this would be accompanied by the remodeling of the parent artery by endovascular embolization with an embolic agent. However, the use of platinum coils to treat large, wide-necked intracranial aneurysms often requires repeat treatment due to coil compaction, as well as the use of a stent to prevent migration to nearby vessels [20][21]. Liquid embolic agents achieve homogeneous and complete filling of aneurysms as opposed to coils. Furthermore, infectious aneurysms are often irregular in shape, making endovascular embolization with liquid embolic agents ideal [22].

The most common complications after endovascular aneurysm repair are type I and type II endoleaks, characterized by the persistent perfusion within the aneurysmal sac. Type I endoleaks result from an inadequate seal and can be seen either at the proximal end of the graft (type Ia) or at the distal end of the graft (type Ib) [23]. The occurrence of type I endoleaks are reported in the range of 2.9–6.9%, whereas type II endoleaks occur more frequently, ranging between 10–45% of all EVAR processes [24]. Type I endoleaks require immediate treatment to prohibit the risk of sac rupture, whereas type II endoleaks are correlated with sac reperfusion caused by collateral vessels. About 40–58% of cases are not associated with sac enlargement and resolve spontaneously [24]. Although transcatheter embolization is generally accepted as the primary treatment option for type II endoleaks, it has not been popular for the treatment of type I endoleaks [23]. However, several clinical studies are being performed to use transarterial embolization as a treatment option for type I endoleaks [24]. Patients require follow-up CT imaging to assess the aneurysm sac size, size of the nidus, diameter of the feeding and draining vessels, and the diameter of the feeding collateral artery to determine if intervention is necessary.

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