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Endovascular embolization using hydrogel microspheres

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Controlled alkaline hydrolysis of crosslinked poly(methyl methacrylate) (PMMA) microspheres produced highly hydrophilic, smooth, compressible, nearly perfect microspheres having a range of water content 40–95%. These particles were found to possess many desirable properties as a material for therapeutic embolization. After successful toxicological and animal evaluation, these particles were used to treat various ailments such as arteriovenous malformations (AVM) of the brain, spinal cord, limbs, face and trunks, pre-operative devascularization of tumours and in the management of severe life-threatening haemoptysis and haematemesis in clinical trials involving over 90 patients at this Institute. The results of these studies appeared to be very encouraging. The material is found to be an ideal embolic agent in all these clinical situations.

1. Introduction

Embolization is a widely accepted mode of management for a variety of vascular lesions such as malformations and vascular tumours in a number of locations [1–4]. Embolic agents, both liquid and particulate, each with its own advantages and disadvantages, have been used to attain this objective [5]. These agents must be delivered to the required site through catheters, the lumen of which ranges from 300 μm to 1 mm. The ease of delivery and the absence of degradability and tissue reaction are the important determinants of an ideal embolic agent. While delivery of liquid embolic agents (e.g. cyanoacrylates) through small catheters is easy, gluing of the catheter tip to the cast of the embolic material is a frequent problem [5]. The delivery of particles through catheters is more difficult, which is an important limitation for the use of currently available particulate embolic agents such as poly(vinyl alcohol) foams, gelatin sponges, lyodura, etc. Hence, we developed a novel, inert, non-biodegradable particulate agent by controlled alkaline hydrolysis of crosslinked PMMA microspheres [6]. These microparticles, which can be prepared in a wide size range (70–2000 μm) are perfectly smooth, slippery, spherical, and highly compressible and can be delivered easily through microcatheters without obstructing the catheter lumen. The application of this material in various clinical conditions and its advantages over other particulate agents are highlighted in this report.

2. Materials and methods

Crosslinked PMMA spheres prepared by a modified suspension polymerization technique of Hart [7] were subjected to alkaline hydrolysis to obtain hydrogel microspheres of desired water content as reported elsewhere [6]. Microspheres retained their demensional stability depending on the degree of hydrolysis. Using test sieves, hydrogel spheres of various sizes were separated in wet condition and washed free of all impurities and air dried. Sterilization of the spheres was achieved by autoclaving at 120 °C for 30 min. No damage to the microspheres was seen on microscopic examination. The biocompatibility of the microspheres was assessed by cell culture and subcutaneous implantation studies as reported previously [8, 9]. The occlusion effect produced by the microspheres has been studied in a dog model by embolizing the renal artery of mongrel dogs over a 1-year period [10].

The above material has been used in a variety of clinical conditions in over 90 patients. The application of the material was predominantly found as a definitive treatment in the management of: (1) central nervous system AVM such as dúral or pial AVM of the brain and the spine, and arteriovenous fistulae such as Type IV carotid cavernous fistula; (2) as a palliative or pre-operative devascularization measure in patients with (a) cranio facial AVMs such as mandibular, maxillary, earlobular and orbital AVMs, (b) peripheral AVMs such as AVMs of the hands, fingers and legs and AVMs in the gluteal and genital regions; (3) in the pre-operative devascularization of intracranial andextracranial tumours; and (4) life-threatening haemoptysis and haematemesis.

All patients underwent an angiographic evaluation prior to embolization to decide on the number of vascular pedicles to be embolized, the size of the nidus of AVM, and the degree of arteriovenous shunt or tumour vascularity. All intracranial and spinal AVMs

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and tumours required superselective catheterization of the feeders/pedicles using either Magic (Balt, France) or Tracker catheters (Target Therapeutics, USA) following a retrograde femoral artery catheterization. The craniofacial AVMs also required superselective catheterization of lingual, ascending pharyngeal, maxillary and occasionally thyro and costocervical trunks through a Bernstein (USCI, CR Brad, USA) catheter. The peripheral AVM also required superselective catheterization; the route and the catheter used were modified depending upon the individual situation. The embolization of patients with haemoptysis required selective catheterization of the bronchial or aorto-pulmonary collateral arteries using a 5F right coronary catheter. Selective catheterization of branches of coeliac axis and superior mesenteric artery were required for embolizing patients with gastrointestinal haemorrhage.

Based on the angioarchitecture of the lesion, appropriate size of hydrogel particles (70–1250 μm) were chosen. The correctly sized sterile hydrogel particles (1 g) were placed in a bowl containing saline and kept for 3–5 min to attain equilibrium swelling. The completely non-aggregatory particles were aspirated into a 2 ml syringe and injected into the feeding pedicles. Check angiograms were performed after each injection of the material to monitor the effect of embolization, the end point being complete disappearance of vascularity.

3. Results and discussion

Hydrogels as a class of materials have been well recognized for their biocompatability due to their close resemblance to living tissue because of the high water content, softness and flexibility. They have been found to be useful in the controlled release of drugs, for immobilization of enzymes, for immunochemical studies, for the propagation of mammalian cells in culture, for coating vascular stents for producing endovascular grafts and in gel permeation chromatography [11]. In recent years, hydrogel particles based on poly(2-hydroxyethyl methacrylate) (PHEMA) have been found to be useful as an embolization agent [12]. We have recently reported on a novel suspension polymerization technique for the preparation of highly porous PHEMA microspheres of wide size range using polymeric porogens [13] which are succeptible to derivatization to a very significant extent due to their high porosity [14], which may also find application as particulate emboli.

Unlike PHEMA, which absorbs only around 40% water at equilibrium, the hydrolysed PMMA microspheres prepared from crosslinked PMMA absorbed large amounts of water (> 95%) depending on the degree of hydrolysis, and remained dimensionally stable even at such high water content, thereby demonstrating that the crosslinks were not completely hydrolysed. The kinetics of hydrolysis with respect to particle size, crosslinking density, alkali concentration, etc. have been reported in detail [6].

While PHEMA microspheres with very high porosity were not found to be compressible, the hydrogel spheres with high water content were found to be extremely compressible without undergoing any damage. For example, delivery of particles having an average diameter of 350 μm (300–400 μm range) could be effected through a Teflon catheter having an internal diameter of 230 μm without causing any damage to the particles.

Particles having an equilibrium water content of around 95% and a carboxyl content of about 40% were employed for embolization. The embolization of intracranial AVMs [15] showed successful results in selected patients (Fig. 1). Since the material is compressible, particles larger than the inner catheter lumen could be injected without any problem. However, there is a limitation in the delivery of large particles through microcatheters which limits its use in treatment of cerebral AVMs. Since the AVM contains unrecognized arterio-venous shunts, the smaller particles may escape the nidus, accounting for the frequent failure rate in these conditions. With improvement in catheter technology giving wider inner lumen catheters, it is hoped to improve the results. Since the hydrogel is extremely slippery, smooth and hydrophilic, catheter blockage has never been a problem, unlike other particles such as lyodura, gelfoam and poly(vinyl alcohol) because of their irregular shape and non-compressible characteristics. We have not observed even a single instance of catheter blockage due to clogged particles during the course of this investigation.

As against cerebral AVM, only smaller particles (100–500 μm) are needed to devascularize intracranial

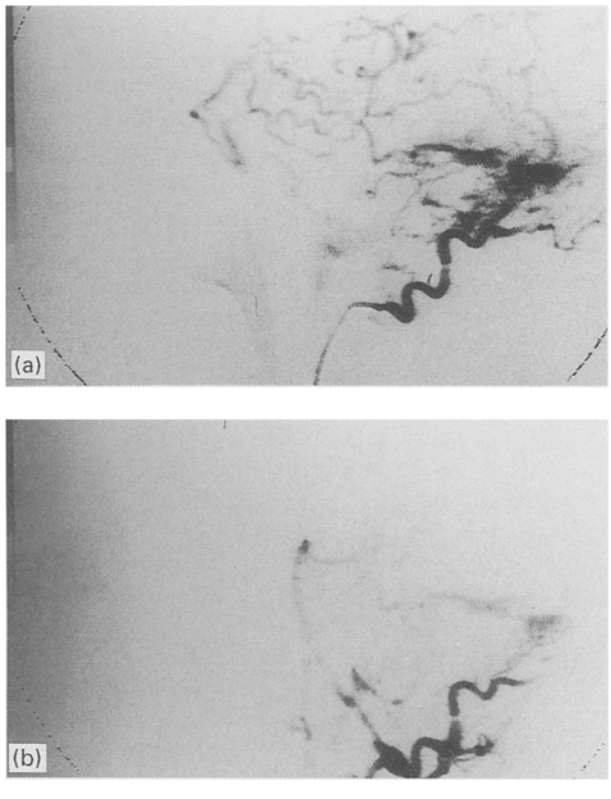

Figure 1 Dural AVM at the level of transverse sinus supplied by occipital artery (a) and following embolization there is obliteration of the AVM (b). Note the filling of vertebrobasilar system through hidden occipitovertebral communication.

tumours such as neurofibroma, meningiomas or haemangioblastomas prior to surgery [16, 17]. These agents are highly suited for these conditions (Fig. 2). Resected specimen following tumour embolization revealed total obliteration of the vascular bed of the tumour without any inflammatory or foreign body giant cell reactions, confirming the inertness of the material as found in the animal experiments [9, 10, 18]. The material is found to be non-biodegradable even after 12 months as against the popular n-butyl cyanoacrylate [19].

Experience with craniofacial AVM shows a high success rate is obtaining satisfactory devascularization prior to surgery thereby reducing operation time and

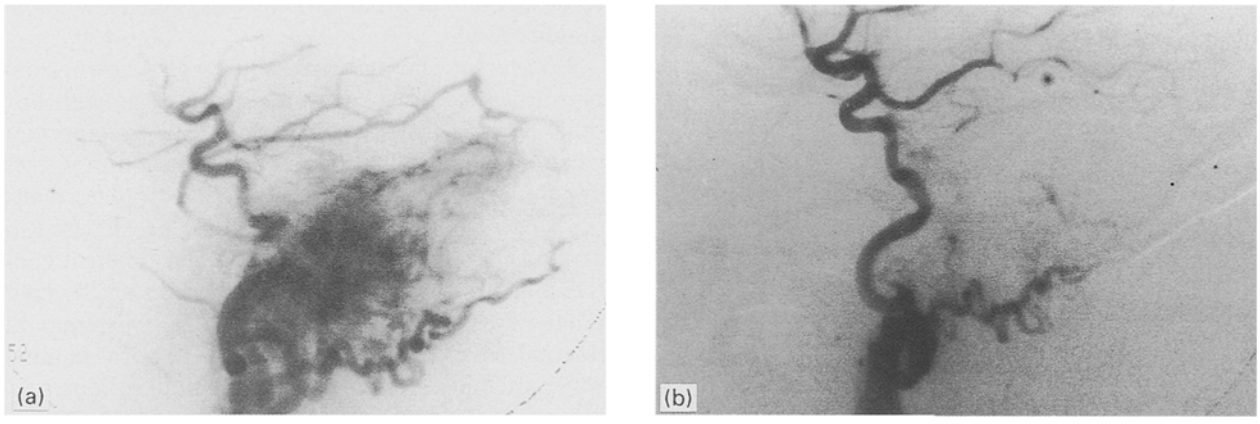

Figure 2 Hypervascular meningioma in the posterior fossa supplied by external carotid branches (a) and total obliteration of vascularity following embolization with hydrogel (150–300 μm) particles (b).

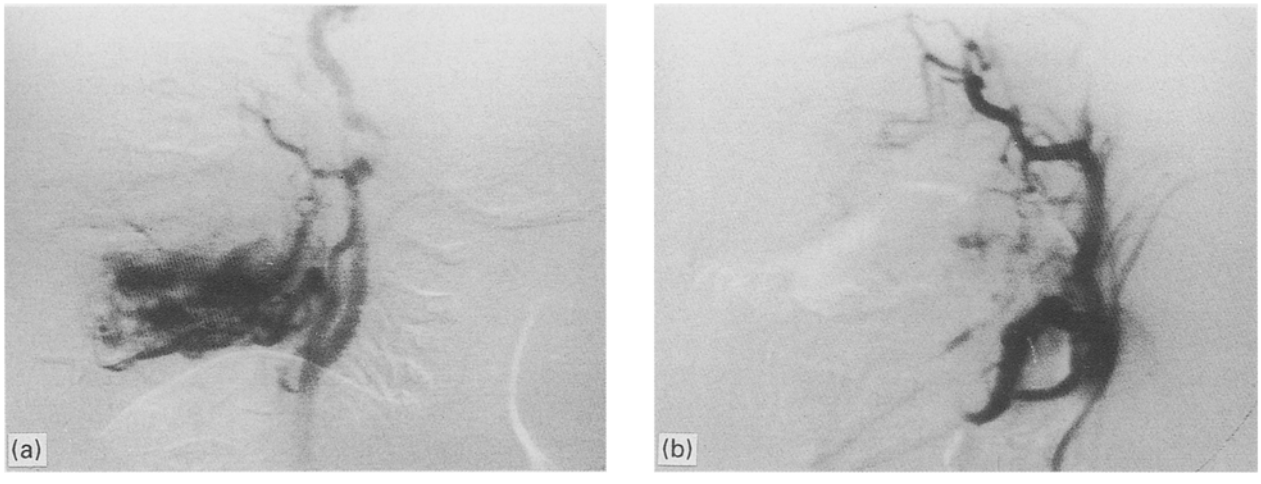

Figure 3 Mandibular AVM supplied by the linguofacial trunk (a) and obliteration of the AVM following embolization with hydrogel (300–500 μm) particles (b).

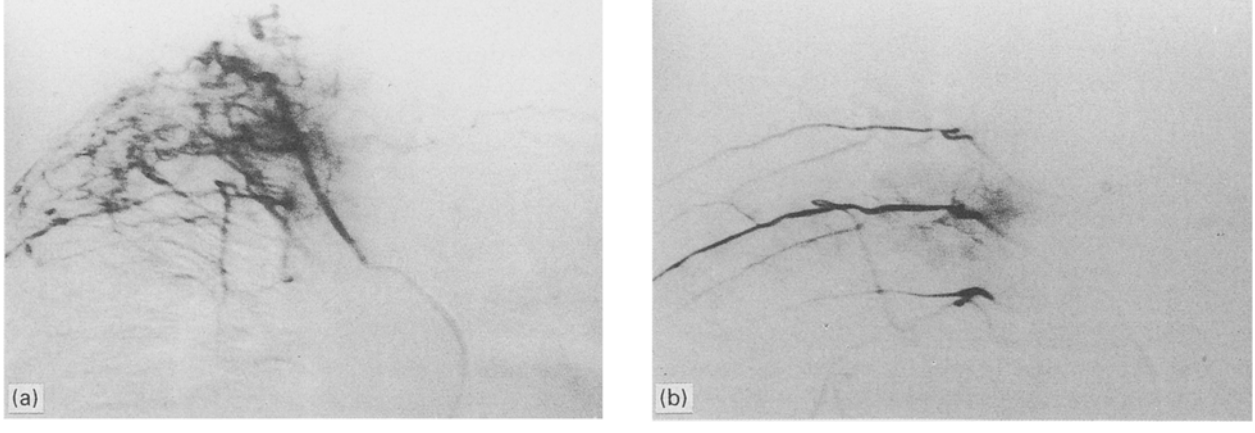

Figure 4 Abnormal neovascularity in the right lung in a patient who presented with haemoptysis (a) and disappearence of abnormal vascularity on embolization (b). Patient is symptom-free.

blood transfusion [20, 21]. AVMs in certain inoperable sites offer good palliation and arrest the progress of the disease following embolization (Fig 3).

Embolization of the bronchial or aortopulmonary collaterals in life-threatening haemoptysis was also found to be extremely effective in tiding over the crisis and giving easier and safer surgery (Fig 4). In certain patients it offers a permanent cure for haemoptysis [22]. Similar gratifying results were also obtained in patients with massive uncontrollable haematemesis or malena, due to angiomatous malformation of the gut wall.

AVMs of the peripheral regions such as hand, leg, gluteal and genital regions are extremely complex containing innumerable feeding pedicles. Careful catheterization of these feeding pedicles and embolization is necessary to obtain a satisfactory result (Fig 5). Often this requires multiple sessions of embolization. The treatment offers good palliation and functional result in spite of an apparently unsatisfactory angiographic result.

Non-target embolization is the best-known complication that can occur with hydrogel as with any other embolic material. This is particularly important when attempting intracranial embolization of AVMs or tumours, where it can lead to catastrophic results [23]. Extreme care and caution must be exercised to avoid such complications. Careful and frequent control angiograms are necessary to decide on the endpoint of embolization. The opening of external to internal carotid pathway should also be borne in mind while attempting external carotid embolizations.

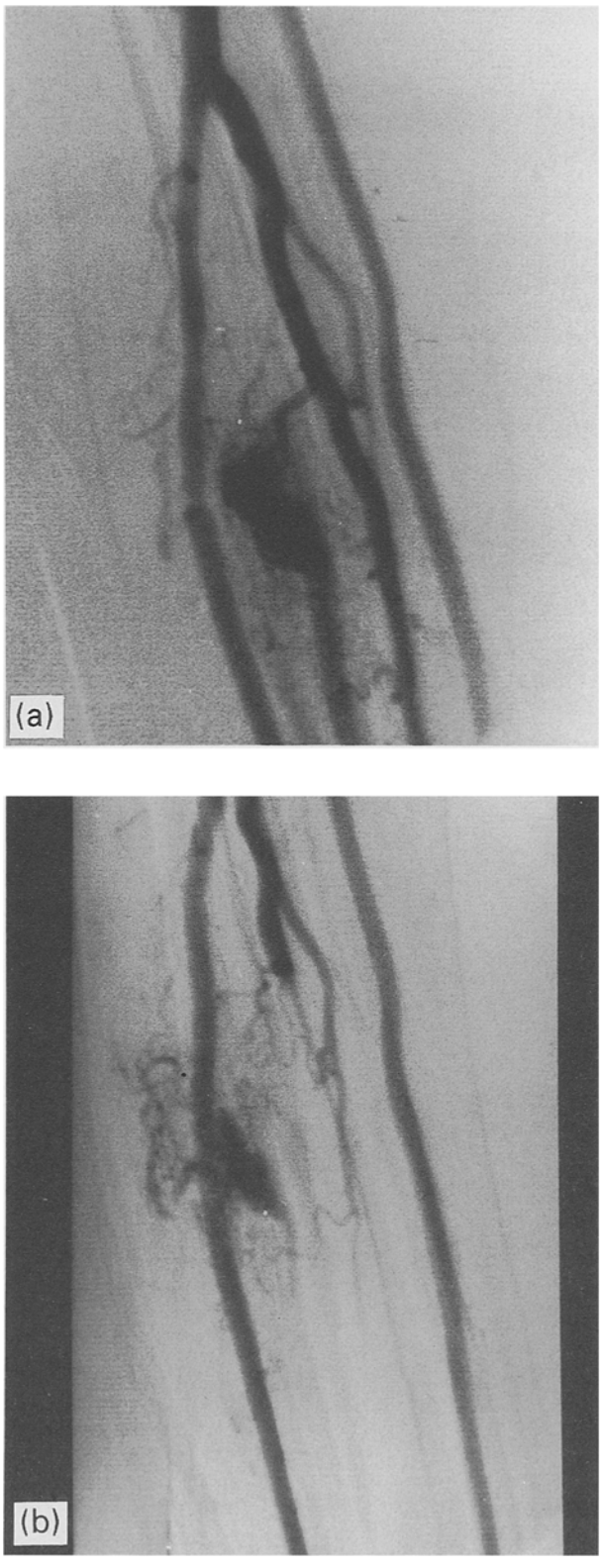

Figure 5 Fore-arm AVM supplied by the interosseus artery (a) and reduction in vascularity following embolization (b).

4. Conclusions

The biocompatability, inertness and non-biodegradability of hydrogel particles made from crosslinked PMMA microspheres by controlled alkaline hydrolysis makes them an ideal embolic agent in treating various tumoral and non-tumoral vascular malformations of the body. The extreme hydrophilicity and compressible characteristics of the emboli help to deliver them easily even through a microcatheter. Embolization with this material offers the desired results in intracranial and extracranial tumours, craniofacial and peripheral AVMs and in the management of life-threatening haemoptysis and haematemesis. The role of this material in the treatment of intracranial vascular malformation is yet to be standardized.

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