Intracarotid hydroxyethyl methacrylate solution causing stroke in dogs

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Hydroxyethyl methacrylate (HEMA) has been advocated as a polymerizing solution with which to prevent deflation of detachable balloons in interventional neuroradiology. It is pertinent to know if unpolymerized HEMA would have untoward effects if accidentally released into the carotid artery by balloon rupture or deflation. Seven mongrel dogs underwent transfemoral catheterization of the common carotid artery and subsequent injection of HEMA solution in volumes of 1 cc in five dogs, 2 cc in one, and 4 cc in one. Angiography performed at the time of injection revealed evidence of intravascular thrombosis as well as possible spasm. Three surviving animals were sacrificed at 48 hours; the brains were fixed and examined histopathologically. One brain was normal and one was autolyzed and could not be examined. Five of the seven animals had histopathologically documented cerebral infarctions of varying size. No foreign substance was seen within the blood vessels to suggest intravascular polymerization. The animals injected with 2 or 4 cc HEMA solution did not survive 48 hours. Literature review reveals little documentation of the toxicology of intravascular HEMA. With its increasing popularity as a compound for polymerization in detachable balloons introduced into the brain, further investigations are warranted to understand the physical properties of the compound and potential risks of its use.

KEY WORDS • balloon embolization • hydroxyethyl methacrylate • stroke • dog

One of the technical problems encountered with the introduction of detachable balloon therapy has been the partial or complete deflation of balloons filled only with contrast or other liquid medium. One possible remedy is to fill the balloon with a solution that is liquid during its introduction but which subsequently polymerizes, yielding a solid ball of polymer which cannot deflate, even upon rupture of the balloon shell. One such material, hydroxyethyl methacrylate (HEMA), has become widely used for this purpose and is currently the material of choice in most centers. Production of the polymer requires mixing the monomer with a crosslinking agent, polyethylene glycol dimethacrylate. This mixture is then combined with a free radical initiator (hydrogen peroxide) and a water-soluble accelerator (ferrous ammonium sulfate). If mixed properly, time to polymerization varies from roughly 15 to 60 minutes in accordance with the relative concentrations of mixture, initiator, and accelerator. If mixed improperly, polymerization may not occur.

We sought to establish the safety of liquid HEMA released into the carotid circulation, as could happen if a balloon filled with HEMA ruptured during placement or if a balloon inflated with unpolymerized HEMA deflated subsequent to detachment. It has been believed that the liquid, if released prior to formation of polymers, would pass through the cerebral vasculature and be excreted by the kidneys without potential harm. Therefore, it has been argued that the balloon could be released either while the material was still liquid or following solidification, as long as detachment was not attempted during the partially polymerized phase of HEMA. Since we could find no documentation of the effect of intracarotid administration of any HEMA compound, the current study was designed to assess whether there are adverse effects or whether the liquid is simply cleared.

Materials and Methods

Since we have experience with canine models of cerebral infarction, we chose the dog as our subject. Although the dog’s internal carotid artery is small, the common carotid artery is large and roughly equal in diameter to the human internal carotid artery. While internal carotid artery administration might have been preferable, significant technical difficulties would have been encountered in selecting a dosage of HEMA analogous to that used in the human and in reliable delivery without surgery. Also, administration of microfibrillar collagen in the common carotid artery of the dog can...
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**TABLE 1**

*Summary of results in seven dogs receiving HEMA injection*

<table>
<thead>
<tr>
<th>Animal</th>
<th>HEMA Injection</th>
<th>Angiographic Findings†</th>
<th>Clinical Findings‡</th>
<th>Pathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 cc</td>
<td>0 hrs: ECA filling defect, ICA occlusion</td>
<td>coma, died &lt; 24 hrs</td>
<td>infarct rt MCA</td>
</tr>
<tr>
<td>2</td>
<td>2 cc</td>
<td>0 hrs: ICA filling defect</td>
<td>coma, died &lt; 24 hrs</td>
<td>infarct rt MCA</td>
</tr>
<tr>
<td>3</td>
<td>1 cc</td>
<td>0 hrs: ICA slowed filling</td>
<td>reduced responsiveness, no focal deficit, swelling on face and neck on side of injection</td>
<td>normal</td>
</tr>
<tr>
<td>4</td>
<td>1 cc</td>
<td>48 hrs: ICA filling defect, ICA slowed filling</td>
<td>severely depressed responsiveness, sacrificed at 24 hrs</td>
<td>autolyzed brain</td>
</tr>
<tr>
<td>5</td>
<td>1 cc</td>
<td>0 hrs: ICA slowed filling</td>
<td>reduced responsiveness, focal deficit</td>
<td>infarct rt MCA</td>
</tr>
<tr>
<td>6</td>
<td>1 cc</td>
<td>0 hrs: ICA slowed filling, ICA luminal irregularity</td>
<td>reduced responsiveness, focal deficit</td>
<td>infarct rt MCA</td>
</tr>
<tr>
<td>7</td>
<td>1 cc</td>
<td>48 hrs: ICA slowed filling but improved</td>
<td>focal deficit</td>
<td>infarct rt MCA</td>
</tr>
</tbody>
</table>

* HEMA = hydroxyethyl methacrylate solution; ECA = external carotid artery; ICA = internal carotid artery; MCA = middle cerebral artery.
† Time of angiogram after HEMA injection is indicated. Luminal irregularity in Animals 4, 5, 6, and 7 was without occlusion or intraluminal filling defect.
‡ "Focal deficit" consisted of hemiparesis, head turning to right, walking in circles, and hemianopsia in response to confrontational testing at 24 and 48 hours. Responsiveness improved at 48 hours in Animal 6, was worse at 48 hours in Animal 7.

produce cerebral infarction; therefore, since common carotid artery delivery produces cerebral delivery, we chose the common carotid artery for this study.

The HEMA was mixed in a standard fashion using a mixture of 50 cc hydroxethyl methacrylate solution (ophthalmologic grade) and 1 cc polyethylene glycol dimethacrylate.* The accelerator compound was made by dissolving 250 mg ferrous ammonium sulfate crystals in 5 cc bacteriostatic water. A combination of 4 cc hydroxethyl methacrylate/polyethylene glycol dimethacrylate was mixed with 2 cc hydrogen peroxide (3% USP solution) and 0.3 cc ferrous solution to give the final concentrations. This solution is termed "HEMA" in this report. The HEMA was mixed in quantities sufficient to deliver the planned dose, with a 2-cc syringeful retained for incubation in a clenched fist to mimic body temperature. The HEMA was observed to polymerize in the incubated syringe in approximately 30 to 40 minutes in all cases. No ferric oxide precipitation was observed in the syringes at the time of the addition of ferrous ammonium sulfate to the HEMA solution.

Seven mongrel dogs, unselected as to size or sex, were anesthetized with approximately 15 mg/kg thioamyl administered intravenously. Following intubation and ventilation with room air mixed with Fluothane (halothane) to maintain general anesthesia, transfemoral catheterization of the right common carotid artery was performed with a No. 5.5 French Hinck 1 catheter. Baseline arteriograms of the common carotid artery were obtained in all dogs prior to injection with HEMA. Filming was performed thereafter at one exposure/sec.

Injections of 6 cc/sec were administered for a total of 8 cc of 60% iothalamate meglumine solution (Conray-60).† Following fluoroscopic verification of catheter placement approximately 2 cm proximal to the origin of the internal carotid artery, volumes of the HEMA solution as summarized in Table 1 were injected by slow push. The catheter was flushed with saline and angiography was repeated immediately.

Following angiography, the femoral catheter was removed and the anesthesia was withdrawn. Upon return of spontaneous respiration, artificial ventilatory support was discontinued. The animals were taken to the recovery area of our animal resources center for postoperative care. Neurological examinations were performed at 24 and 48 hours following injection of HEMA. The animals were observed for reduced responsiveness, hemiparesis, walking in circles ("circling"), posturing with the head turned to the injected side ("head turning"), and hemianopsia. Hemianopsia was tested via confrontational stimulation in each visual hemifield. A blinking response to threatening stimulus (waving fingers) presented to the right side, but no response to stimuli to the left side, was scored as a left homonymous hemianopsia. Follow-up arteriograms were obtained at 24 hours in one animal and at 48 hours in three animals. The other three animals did not survive for follow-up angiography or for a 24-hour neurological examination.

Three animals surviving 48 hours were sacrificed at that time by an intravenous Pentothal (thiopental) overdose. The brain of each animal was removed at the time of death and placed in 10% phosphate-buffered neutral formalin. After a minimum of 48 hours of immersion fixation, the brains were sliced at 10-mm immersion fixation, the brains were sliced at 10-mm

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* Polyethylene glycol dimethacrylate supplied by Polysciences, Inc., Warrington, Pennsylvania.
† Crystals supplied by EM Industries, Cherry Hill, New Jersey.
‡ Iothalamate meglumine solution supplied by Mallinckrodt Medical, Inc., St. Louis, Missouri.
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FIG. 1. Baseline (left) and postinjection (right) arteriograms of a dog injected with 4 cc hydroxyethyl methacrylate solution (Dog 1). Postinjection, multiple large intraluminal filling defects (short arrows) have developed and the proximally occluded internal carotid artery is filling via the maxillocarotid anastomosis (long arrow).

intervals in the coronal plane and photographed. Slices were then dehydrated in alcohol and xylene, embedded in paraffin, mounted on oversized glass slides, stained with hematoxylin and eosin, coverslipped, and examined with a light microscope.

Results

Clinically, the animals responded in accordance with the dosage administered, varying from death without awakening from anesthesia (doses of 2 or 4 cc) to a syndrome of immediate poor responsiveness and hemiparesis with responsiveness improved by 48 hours. One animal had no focal deficits, although reduced responsiveness was noted as well as swelling of the face and neck on the side of injection. These results are summarized in Table 1.

angiographically, large intraluminal filling defects were seen at high doses of HEMA (Fig. 1) and distal internal carotid artery irregularity or occlusion was seen at the lower doses (Fig. 2). All animals demonstrated immediate angiographic abnormalities, consisting at least of slowed filling of the internal carotid artery relative to its baseline state.

Histopathologically, five of seven brains demonstrated acute cerebral infarction in the hemisphere on the side of injection without corresponding changes in the opposite hemisphere (Fig. 3). The infarcts were characterized by pale-staining, eosinophilic, necrotic neurons, congested small blood vessels with occasional foci of extravasation of blood into the parenchyma, cellular infiltration by acute inflammatory cells, and vacuolation and pallor of the neuropil (edema). All infarcts involved the right middle cerebral artery territory, and in three specimens portions of the anterior cerebral artery territory were also involved. One brain (Dog 3) was grossly and histologically normal. This animal had severe swelling of its face and neck on the right side at 24 and 48 hours. Another brain (Dog 4) was too autolyzed to be adequately evaluated pathologically.

Although the HEMA polymerized normally in the syringes, the mechanism for the toxic response was unknown. Since it was injected in the liquid state prior to polymerization or partial polymerization in the syringe, one possible explanation might be that it became partially polymerized on contact with blood. The microscopic sections were therefore reviewed specifically for evidence of intravascular polymerization or apparent foreign bodies. No definite thromboembolic material that might have corresponded to polymer formation was identified in any of the blood vessels of any dog.

Discussion

Methacrylate compounds have widespread uses in medicine, varying from contact lens production to tissue embedding for pathological examination. Some investigators have shown skin sensitization to hydroxyethyl methacrylate used as a component in anaerobic sealant and to 2-hydroxyethyl methacrylate used as an acrylic monomer in printing plates.

Little is known of its effects if administered in vivo. Imai and Masuhara found that poly(hydroxyethyl methacrylate) caused tumors when implanted in rats,
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while no tumors were seen in hamsters or guinea pigs. These changes corresponded to the thickness of capsule formation around the implant. An intracorneal lens implant recovered 6 months after implantation in a patient\textsuperscript{40} did not show evidence of inflammation or neovascularization. Detailed long-term studies of the biocompatibility of HEMA as mixed for this study could not be found. No prior studies of the effect of \textit{in vivo} administration of nonpolymerized liquid HEMA compounds were identified. Now that this agent is widely used for polymerization in detachable-balloon therapy, the pharmacodynamic characteristics of HEMA are becoming more important. Since balloon walls deteriorate over time, exposing the contents to the bloodstream, the effects of both liquid and solid HEMA are pertinent.

The mechanism of the strokes caused in this series is also unclear. It is unknown whether HEMA had a direct toxic effect on the brain or whether some component of the solution was at fault. As peroxide is known to have hemolytic properties, perhaps red cell fragments or clumps occluded small vessels, while the HEMA itself was not the causative factor. It was not the purpose of this study to examine the pathophysiology in depth; rather, the investigation was designed solely to document the presence of any toxicity in the HEMA compound.

This study underscores the hazards of casual use of this material. However, there are no good, proven alternative compounds for use in detachable balloons where deflation over time carries its own set of risks. The severity of the disease in question must also be considered in assessing acceptable risks. This study underscores the need for additional basic research in order to establish a more ideal compound.

Acknowledgments

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