Neurosurgical forum
Letters to the editor

Hydroxyethyl Starch

To The Editor: We have read with great interest the letter by van den Brink, et al. (van den Brink WA, van Genderen P, Thijssen WJ, et al: Heterastach coagulopathy. Letter. J Neurosurg 85:367, August, 1996). The authors informed us via telephone that the hydroxyethyl starch (HES) used by them was Elohaest. Elohaest is one of the three medium molecular weight (MW) HES 200s we have studied (Treib J, Haass A, Findur G: Heterastach coagulopathy. Letter. J Neurosurg 85:367–368, August, 1996). Elohaest is the starch with a degree of substitution of 0.62 and a C1/C6 ratio of 10. Because of its high degree of substitution and C1/C6 ratio, the body’s α-amylases only slowly degrade this starch intravascularly. For this reason, Elohaest has the highest in vivo MW of all three HES 200s we have studied. It also leads to the largest increase in partial thromboplastin time and to an 80% drop in the factor VIII/von Willebrand factor complex. The hemorrhagic complications observed by Dr. van den Brink therefore confirm the clinical relevance of our studies. By using a HES with a lower MW, these hemorrhagic complications can be avoided.1,3

We have to agree with Dr. Muizelaar (Muizelaar JP: Response. J Neurosurg 85:368, August, 1996) that, unfortunately, starches with a low in vivo MW are not available everywhere in the world. In this respect, Germany’s drug and approval laws are more liberal, and a variety of different HESs are in use in Germany. The current drug register of the German federal association of pharmaceutical companies lists 18 different kinds of HES, manufactured by five different companies. Of these, two solutions have a high in vitro MW (450 kD), 11 have a medium MW (200 kD) and three a low MW (40–70 kD). In addition to different in vitro MWs, these starches have different degrees of substitution (0.4–0.7) and different C1/C6 hydroxyethylation ratios (3–13).

Before discussing the differences between the different starches, it is necessary to elaborate on the chemical structure of HES. Hydroxyethyl starch is a high polymeric glucose compound. It is manufactured through hydrolysis and subsequent hydroxyethylation from the highly branched starch amylopectin. Hydroxyethyl starch consists of glucose units that are connected within the chain through α-1,4 glycosidic bonds and through α-1,6 glycosidic bonds at the branching points with the hydroxyethyl groups. Originally, HES was only characterized by the initial in vitro MW, that is, the median MW in the infusion solution; however, this simple characterization is not sufficient, because HES is degraded in vivo by α-amylases, independently of the in vitro MW.

The degree of substitution indicates the average number of hydroxyethyl groups per glucose unit. Hydroxyethyl starch 200/0.62 therefore has a median MW of 200 kD and 62% of its glucose units have a hydroxyethyl group. The α-amylases can only degrade unsubstituted glucose units. By changing the degree of substitution, it is possible to vary the degree of enzymatic breakdown and to exert control over the extent and duration of the volume effect.1 Some of the very highly substituted molecules cannot be metabolized at all, in which case the degree of substitution becomes a limiting factor.

Because the glucose units can be substituted at C2, C3, or C6, different substitution patterns are possible. The substitution pattern is described through the C1/C6 hydroxyethylation ratio. The higher this ratio, the higher the share of hydroxyethylated starches that are substituted at C6. Also, the higher this ratio, the less the starch is metabolized, which leads to a different in vivo behavior of the starch.4

The pharmacological differences between the individual starches are clinically relevant for several reasons, outlined as follows: contrary to widespread opinion, we were able to show in several recent studies that hemorrhagic complications after the infusion of larger volumes of HES can be avoided if a starch with a low in vivo MW is administered. This is due not only to a smaller effect on the coagulation system and the subsequent avoidance of an acquired Type I von Willebrand syndrome4 but also to a smaller decrease in platelet volume, because platelet volume and platelet function are positively correlated.5 In addition, HES with a low in vivo MW has better rheological characteristics than HES with a high in vivo MW, because high MW macromolecules affect plasma viscosity and erythrocyte aggregation negatively (Table 1).1,6 This could explain the poor outcome of the patients treated with high MW HES (HES 480/0.7) by Dr. Muizelaar.

Our latest studies indicate that HES with a low in vivo MW has a smaller negative effect on fibronectin and the reticuloendothelial system (RES). This is because molecules that are too large for renal elimination are eliminated via the RES.6 The most frequent side effect of HES, therapy-resistant itching due to the accumulation of starch molecules in the skin, can probably also be avoided through the use of noncumulating starches.

High- and medium-MW HES with a high degree of substitution (> 0.5) or a high C1/C6 ratio (> 6) and their resulting high in vivo MW should only be administered if a long-lasting volume effect is desired and no hemorrhagic complications are expected. In all other cases, low-substitute HES with a small C1/C6 ratio and a consecutive low

<table>
<thead>
<tr>
<th>In Vitro MW</th>
<th>Substitution</th>
<th>C1/C6 Ratio</th>
<th>In Vivo MW</th>
<th>Plasma Viscosity (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.5</td>
<td>3</td>
<td>57.5</td>
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</tr>
<tr>
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<td>6</td>
<td>84.1</td>
<td>+3.1</td>
<td>NS</td>
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<tr>
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<td>13</td>
<td>95.0</td>
<td>+10.1</td>
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<tr>
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<td>10</td>
<td>120.6</td>
<td>+18.5</td>
<td>&lt;0.01</td>
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</tbody>
</table>

* Prior to Day 10 of treatment. Abbreviation: NS = not significant.
in vivo MW (40–70 kD) should be used. These low in vivo MW HESs do not accumulate, even after repeated administration, and have better effects on blood clotting and RES, as well as on the rheological parameters plasma viscosity and erythrocyte aggregation.

**References**


**Edema, Thrombin, and Dexamethasone**

To The Editor: In regard to a recent article by Colon, et al. (Colon GP, Lee KR, Keep RF, et al: Thrombin-soaked gelatin sponge and brain edema in rats. *J Neurosurg* **85**:335–339, August, 1996), the authors demonstrated that the brain water content of rats that had undergone cortical resection and application of a thrombin-soaked sponge was greater than in those that had had the gelatin sponge alone applied to the resection bed. Moreover, addition of hirudin, a thrombin antagonist, to the thrombin-soaked gelatin sponge seemed to negate the thrombin effect. The authors concluded that “topical thrombin should not be in contact with brain parenchyma because it may contribute to significant peri- and postoperative edema . . . and thrombin should be applied only if all other options have been attempted and bleeding persists.”

Although the animals in this study did not receive perioperative dexamethasone, this agent is frequently used in clinical practice, especially if parenchymal resection is contemplated. Because dexamethasone may influence the degree of edema formation, it is possible that the thrombin effect demonstrated by Colon, et al., may be significantly reduced or even nonexistent in that patient population. This is an interesting study that provides relevant information. Although it is possible that the perioperative use of dexamethasone would not have significantly altered these findings, I believe that their conclusions would have been better supported if the study had addressed this issue.

**RESPONSE**

We very much appreciate Dr. Abdou’s comments regarding our article on thrombin-soaked gelfoam. Our work on the edemogenic effect of thrombin is a sequel to previous work on the brain edema caused by intracerebral hemorrhage (ICH) and its breakdown products. In our clinical evaluation of patients with ICH, we, as well as others, have seen marked edema surrounding the resolving ICH bed. We have used dexamethasone without significant clinical or radiological improvement in our patients. Our rationale for this phenomenon is that the edema induced by the resolving ICH is cytotoxic as opposed to vasogenic, and thus peri- and postbleed steroids are of little benefit.

In our laboratory investigations, we have held this line of thinking and have not further pursued the effects of perioperative dexamethasone in our rat model. However, we recognize that the use of perioperative steroids is commonplace and perhaps their inclusion in our rat model would have been clinically relevant.

**Split Dura for Revascularization**

To The Editor: The article by Shiro Kashiwagi, et al. (Kashiwagi S, Kato S, Yashuhara S, et al: Use of a split dura for revascularization of ischemic hemispheres in moyamoya disease. *J Neurosurg* **85**:380–383, September, 1996) presents an excellent addition to present revascularization techniques. The concept of splitting the dura for this purpose is quite innovative. I am curious to know if the authors have considered denuding the smooth inner surface of the dura either chemically or mechanically, in combination with placement of the superficial temporal artery below the dura; such a technique may necessitate a more circumferential incision in the dura. It would expose more surface area for revascularization and would permit vascularization of the superficial temporal artery to the inner aspect of the dura as well as directly to the cortex.

**RESPONSE**

I appreciate Dr. Heifetz’s comments on our new technique for cortical revascularization. His suggestion that more surface area of the dura might be exposed by denuding the angiogenically inactive inner layer is quite intriguing. We could apply his idea to our technique by removing the inner layers instead of folding them into the subdural space. We have not tried denuding the inner surface of the dura chemically because we have no idea what kind of chemical agent is effective for this purpose. As he mentioned, a more circumferential incision in the dura is necessary to denude a wider area of the inner layer mechanically, but I am wary of injuring the natural transdural cortical anastomosis by a large, circumferential dural incision. In our technique, the dural incisions are made in the space between the meningeal arteries so that they are preserved as much as possible. We try to expose more surface area for revascularization by making multiple small splits, rather than one large dural incision. Placing the superficial temporal artery below the denuded dura,