Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury


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Patients with severe head injury frequently have evidence of elevated intracranial pressure (ICP) and ischemic neuronal damage at autopsy. Mannitol has been used clinically to reduce ICP with varying success, and it is possible that it is more effective in some types of head injury than in others. The aim of the present study was to determine the effect of mannitol on ICP, cerebral perfusion pressure (CPP), and cerebral blood flow (CBF) in patients with severe head injury, and to discover if these effects differed in different types of injury. Measurements of CPP, ICP, and CBF were made in 55 patients with severe head injury. In general, the resting level of CBF was higher in patients with diffuse injury (mean 50.2 ml/100 gm/min) than in those with focal injury (mean 39.8 ml/100 gm/min). Mannitol consistently reduced ICP and increased CPP and CBF by 10 to 20 minutes after infusion. The lowest flows (31.8 ml/100 gm/min) were recorded from the most damaged hemispheres of patients with focal injuries and elevated ICP. The baseline levels of flow did not correlate with ICP, CPP, Glasgow Coma Scale score, or outcome. Only four of the 55 patients had a CBF of less than 20 ml/100 gm/min in either or both hemispheres. The few low CBF's in this and other studies may reflect the steady-state conditions under which measurements are made in intensive care units, and that these patients have entered a phase of reperfusion.

KEY WORDS • head injury • intracranial pressure • mannitol • Glasgow Coma Scale • cerebral blood flow • cerebral perfusion pressure

ISCHEMIC brain damage is found in the majority of head-injured patients who die. For this reason, management of severe head injuries has often attempted to improve cerebral blood flow (CBF), for example by increasing the cerebral perfusion pressure (CPP). Nevertheless, there have been few clinical reports of changes in CBF in response to such maneuvers, particularly with reference to different types of injury.

Mannitol is used widely, in varying regimens, in the management of severe head injury, and there is a large body of evidence that indicates that it can reduce intracranial pressure (ICP) in such patients. On the other hand, reported effects of mannitol on mean systemic blood pressure are controversial, with some work suggesting that the drug may produce hypotension with some resultant reduction in CPP. Furthermore, a large multi-center study of head-injured patients has indicated that no benefit is derived from the general use of mannitol in unselected groups of patients with head injury.

It is likely that the effects of any agent differ in different sites within the damaged brain, as well as in different types of head injury. Previous studies have indicated that mannitol can increase CBF in severely injured patients in the acute phase of head injury, but the changes have usually been reported in only one hemisphere, and different types of injuries have not been compared. A consistent relationship between changes in CPP and CBF has not therefore emerged, although this aspect has been well studied experimentally. The aims of the present study were to document the effects of a bolus of mannitol on CBF and CPP in head-injured patients, and to ascertain whether the responses were similar in different diagnostic categories, and in the two hemispheres.

Clinical Material and Methods

A total of 55 patients (mean age 37 years) are included in this study. All had survived for more than 6 hours after head injury, and had been admitted to the...
intensive care unit of the Institute of Neurological Sciences in Glasgow. At the time of CBF measurement 73% were in coma. All had undergone computerized tomography scanning, and ICP monitoring had been instituted. Their CBF was measured within 72 hours of injury or operation. Patients were divided into those with focal and those with diffuse injuries, according to the following criteria. A lesion was regarded as focal if the patient had an intracerebral hematoma of greater than 2.5 cm in diameter, or a subdural hematoma more than 1 cm thick or producing a midline shift of more than 1 cm.

**Intracranial Pressure Measurement**

Ventricular fluid pressure or subdural pressure was measured by a fluid-filled catheter connected to a Statham P23 or P50 pressure transducer connected to a Gould pen recorder for continuous recording.*

**Measurement of Cerebral Blood Flow**

Bilateral simultaneous CBF measurements were made from two large sodium iodide crystal scintillation detectors (50 mm in diameter) arranged in parallel and aimed in an anteroposterior direction from the frontal region above the frontal sinus. The xenon-133 (133Xe) intravenous method was used, with subtraction of the end-expiratory 133Xe curve from the brain clearance curves to correct for recirculation. End-expiratory 133Xe concentrations were measured by sampling gas obtained from the endotracheal tube or via a tightly fitting face mask. An exit tube and a room fan were used to eliminate xenon gas from the patient area. A bolus dose of 10 mCi of 133Xe was given intravenously, and clearance curves were monitored for 10 minutes. Resting hemispheric CBF was measured before the administration of mannitol. In general, global CBF is expressed as the mean value for the two hemispheres. Where indicated in the text and tables, the two sides were recorded separately in this study: in focal injuries they were expressed as the more and the less damaged hemisphere (the distinction made from radiological and operative findings), and in diffuse injuries as left and right.

**Level of Consciousness and Outcome**

The level of consciousness at the time of CBF measurement was recorded using the Glasgow Coma Scale, and outcome at 6 months is expressed using the Glasgow Outcome Scale. 9

**Measurement of Physiological Variables**

Arterial blood gases were measured on a Corning 175 blood gas analyzer. End-expiratory carbon dioxide was measured on a Goddart capnograph.† Mean systemic blood pressure (MBP) was recorded with a sphygmomanometer cuff or by an arterial line connected to a Statham P50 pressure transducer connected to a Gould pen recorder for continuous recording. The CPP was calculated as the difference between MBP and ICP at the time of each CBF measurement.

**Administration of Mannitol**

A bolus of 20% mannitol (0.25 to 0.5 gm/kg) was given intravenously over 10 to 15 minutes. Measurement of CBF was initiated 10 to 20 minutes after the mannitol infusion was completed, and MBP and ICP were recorded at the time of the 133Xe injection.

**Statistics**

Resting flow values and ICP and CPP measurements were available in 55 patients. Full documentation of ICP, CBF, and CPP after completion of the mannitol infusion was available in 41 patients. All values are...
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Fig. 2. Resting cerebral blood flow (CBF) in patients with diffuse and focal injuries did not correlate well with either intracranial pressure (ICP) or cerebral perfusion pressure (CPP).

expressed as means ± standard errors of the mean. Comparisons were made with Student's paired or unpaired t-tests and differences were considered significant when p < 0.05.

Results

Of the 55 patients, 33 (60%) had focal injuries and, of these, nine (27%) were studied while undergoing ICP monitoring to aid in deciding whether surgical removal of a hematoma was required.

Resting Cerebral Blood Flow

The mean CBF for all 55 patients was 43.9 ± 2.4 ml/100 gm/min. The 33 patients with focal injuries had a mean flow of 39.8 ± 2.7 ml/100 gm/min and the 22 with diffuse injuries had a mean flow of 50.2 ± 4.1 ml/100 gm/min. The mean CBF was significantly higher in the diffuse-injury group than in the focal-injury group, and the distribution of flows indicates the preponderance of lower values in patients with focal injury (Fig. 1). Patients were further divided into groups with low and high ICP, based on the pressure values on the day of CBF measurement. There were 33 patients with an ICP of less than 20 mm Hg (low-ICP group), and 22 patients had pressures above this level. Although mean CBF was higher in the low-ICP group, no significant difference was found between the mean CBF values of the high- and low-ICP groups taken as a whole. This difference was less evident in the diffuse-injury group, and was greatest in patients with focal injuries, where high ICP was associated with the lowest mean CBF (36.1 ± 3.5 ml/100 gm/min) (Table 1). Indeed, the lowest mean CBF was recorded in the most damaged hemisphere of patients with focal injuries and high ICP (31.8 ± 3.2 ml/100 gm/min). In general, however, the resting CBF did not correlate well with either the initial ICP or the CPP (Fig. 2).

In only four patients was CBF below 20 ml/100 gm/min recorded. In one patient with a diffuse injury there was bilateral reduction in flow to 15 and 18 ml/100
Effect of Mannitol

Mannitol consistently reduced ICP and increased MBP. This produced a significant increase in CPP and CBF (Table 2). The increase in CBF with mannitol infusion was slightly greater in patients with diffuse injuries (Table 3) and in the undamaged hemispheres of patients with focal injuries. This increase was also greater when a focal injury resulted from a hematoma that was still present than after it had been removed, although this was not significant. Mannitol infusion produced an increase in CBF in all patients with a very high level of ICP (≥ 41 mm Hg), and consistently resulted in an increase in CBF when CPP was 50 mm Hg or less (Table 4). In patients with diffuse injury, there was a greater increase in CBF in the right than in the left hemisphere (Table 3), and the highest flows were recorded after mannitol in the right hemisphere of diffusely injured patients with high ICP (62.5 ± 10.8 ml/100 gm/min).

In these studies, there was no correlation between the Glasgow Coma Scale score and CBF, either in diffuse or focal injuries (Fig. 3). Similarly, the outcome at 6 months was unrelated to CBF or the type of injury.

Discussion

These studies have documented CBF levels in the two hemispheres of patients with either a diffuse or a focal head injury, and related these to ICP, CPP, and the effect of mannitol. In general, patients with diffuse brain injury had higher levels of CBF than did those with focal injury. The lowest resting CBF values were recorded from the most damaged hemispheres of patients with a focal injury and high ICP. However, resting CBF was not related to initial ICP, CPP, or Glasgow Coma Scale score, and follow-up studies have revealed that it is not related to outcome either. Mannitol consistently increased CBF, and this increase was associated with a corresponding increase in CPP and reduction in ICP.

Very few ischemic flow levels were recorded in our series; four of the 55 patients had CBF of less than 20 ml/100 gm/min. This may be because, at the time of blood flow measurements, patients had been stabilized in an intensive care unit. These observations correspond with those of Overgaard, et al.,20 who also reported a low incidence of ischemic flow values (< 20 ml/100 gm/min) in stable head-injured patients: only 1% of the regions of patients in better outcome categories and 15% of the regions of those who died or remained vegetative had ischemic levels. The few ischemic flows observed were most often seen in the early hours after injury. Our results are also consistent with those of

TABLE 2
Mean CBF, ICP, and CPP in patients before and after mannitol infusion*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Mannitol†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 gm/min)</td>
<td>43.5 ± 3.0</td>
<td>50.2 ± 3.5</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>21.9 ± 1.9</td>
<td>17.2 ± 1.9</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>72.0 ± 2.8</td>
<td>81.7 ± 2.5</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for 41 patients. CBF = cerebral blood flow; ICP = intracranial pressure; and CPP = cerebral perfusion pressure.
† Each value showed a significant difference between control and mannitol values (one-sided paired t-test).

TABLE 3
Mean cerebral blood flow (CBF) before and after mannitol infusion in patients with focal and diffuse injuries*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Cases</th>
<th>CBF (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>global CBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diffuse injuries</td>
<td>18</td>
<td>51.2 ± 4.9</td>
</tr>
<tr>
<td>focal injuries</td>
<td>23</td>
<td>37.4 ± 3.2</td>
</tr>
<tr>
<td>lesion present</td>
<td>9</td>
<td>38.8 ± 4.9</td>
</tr>
<tr>
<td>lesion absent</td>
<td>14</td>
<td>36.5 ± 4.4</td>
</tr>
<tr>
<td>hemispheric CBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>focal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more damaged hemisphere</td>
<td>23</td>
<td>37.1 ± 3.4</td>
</tr>
<tr>
<td>less damaged hemisphere</td>
<td>23</td>
<td>37.8 ± 3.4</td>
</tr>
<tr>
<td>diffuse</td>
<td>18</td>
<td>49.6 ± 4.9</td>
</tr>
<tr>
<td>lt hemisphere</td>
<td>18</td>
<td>52.8 ± 5.1</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means (ml/100 gm/min). The patients with focal injury are subdivided depending on whether the lesion was still present or had been removed, and depending on which hemisphere had been affected.
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Obrist, et al., who observed a high incidence of hyperemia in their patients with acute head injury, and recorded flows of less than 20 ml/100 gm/min in only 14% of their cases. They also showed that all these patients had a reduced cerebral metabolic rate for oxygen (CMRO₂). Indeed, they further demonstrated coupling between CBF and CMRO₂ for patients in their "reduced-flow" group, which included patients with flows of up to 33 ml/100 gm/min; the patients with intermediate levels of flow (20 to 33 ml/100 gm/min) having higher levels of CMRO₂. Enevoldsen, et al., likewise commented on the low incidence of ischemia, and a high frequency of hyperemia.

Our finding that the lowest levels of CBF were in the damaged hemispheres of focally injured patients suggests that hematomas (classified as focal injuries in this study) are associated with ischemic brain damage. This is in accordance with human autopsy studies and recent experimental work, which has revealed profound regional ischemia within minutes of the start of intracranial hemorrhage. It may be that, to record the real extent of areas of such profound ischemia in man, a focal cross-sectional technique for measurement of CBF is required.

FIG. 3. Resting cerebral blood flow (CBF) in patients with diffuse and focal injuries compared with Glasgow Coma Scale (right, 3-15) and Glasgow Outcome Scale (left, 1-5).

Previous reports that characterize CBF patterns in patients with different types of head injury have indicated that diffuse injury is associated with hyperemia more frequently than focal injury. The significantly higher density measurements on computerized tomography reported in patients with diffuse swelling suggests that this hyperemia may be the result of increased cerebral blood volume, but whether changes in volume alone account for the changes in Hounsfield number is in doubt. The mechanism for the increase in CBF that we observed after mannitol administration is uncertain. It may reflect some loss of autoregulation, so that elevation of the CPP leads to a passive elevation of CBF. This is suggested from our data which showed that mannitol consistently increased CBF in patients whose CPP was below 60 mm Hg, the lower threshold for autoregulation. Nevertheless, it is well known that mannitol improves CBF in ischemia without profoundly altering CPP. An alternative explanation for the effect of mannitol may lie in its osmotic effects or in its effects on blood viscosity. The fact that CBF increased in all patients with very high ICP indicates that the osmotic effect may be very important in these cases.
It should be stressed that in our studies the effects were short-term, and may differ considerably from the long-term effects of mannitol or its continued use. Mannitol acts over time to reduce the circulating blood volume and produce hypotension. This may explain why mannitol failed to improve the outcome in a large group of patients with head injury reported by Jennett, et al. Its resuscitative effects on head-injured patients in the acute phase may have to be measured separately from the ultimate outcome. Furthermore, newer techniques for the long-term administration of mannitol may produce a more stable control of ICP. With these techniques, the dosage of mannitol is constantly revised by computer monitoring of the ICP. It seems, therefore, that there is a place for the evaluation of both the acute effects of mannitol and its use with servo-assisted infusion pumps. If the main cause of brain damage in head injury is ischemic, early restoration of the CPP offers the most likely opportunity for therapeutic advance. These hemodynamic effects, however, may not necessarily apply to the more stable resuscitated patient in the intensive care ward, unless an intercurrent reduction in CPP develops secondarily.

This study demonstrates that mannitol is most likely to be of value in patients with focal injuries, in those with very high ICP, and in those in whom the CPP is at or below the lower limit of autoregulation.

Acknowledgment

Our thanks go to Ms. S. Halley for preparing the manuscript.

References


A. D. Mendelow, et al.