Effects of Continuous Hypertonic Saline Infusion on Perihemorrhagic Edema Evolution

Ingrid Wagner, MD; Eva-Maria Hauer, MD; Dimitre Staykov, MD; Bastian Volbers, MD; Arnd Dörfler, MD; Stefan Schwab, MD; Jürgen Bardutzky, MD

Background and Purpose—Mass effect of hematoma and the associated perihematomal edema are commonly responsible for neurological deterioration after intracerebral hemorrhage. Efficacy of surgical and medical therapy is limited. We studied the effect of early continuous hypertonic saline infusion on development of perihematomal edema after severe spontaneous supratentorial hemorrhage.

Methods—Patients with spontaneous lobar and basal ganglia/thalamic bleeding >30 mL (n=26) were treated with early (<72 hours) continuous hypertonic saline infusion (3%) to achieve sodium of 145 to 155 mmol/L and osmolality of 310 to 320 mOsmol/kg. Evolution of absolute edema volume and relative edema volume (ratio absolute edema volume/initial hematoma volume) was assessed on repeated cranial CT and compared to historical patients (n=64) identified on database with hematoma >30 mL.

Results—in the treatment group, absolute edema volume was significantly smaller between day 8 and day 14 ($P_{\text{absolute edema volume}}=0.04$) and relative edema volume was significant smaller between day 2 and day 14 ($P_{\text{relative edema volume}}=0.02$). Intracranial pressure crisis (>20 mm Hg for >20 minutes or new anisocoria) occurred less frequently in the treatment group (12 versus 56; $P=0.048$). In-hospital mortality was 3 (11.5%) in the hypertonic saline group and 16 (25%) in the control group ($P=0.078$). Side effects theoretically associated with hypertonic saline including cardiac arrhythmia and acute heart and renal failure occurred in both groups to a similar extent.

Conclusions—Early and continuous infusion of hypertonic saline in patients with severe spontaneous intracerebral hemorrhage was feasible and safe. The beneficial effect of this treatment regimen on edema evolution and outcome has to be demonstrated in a controlled trial. (Stroke. 2011;42:00-00.)

Key Words: hypertonic saline ■ intracerebral hemorrhage ■ perihemorrhagic edema

Spontaneous intracerebral hemorrhage (ICH) is usually associated with high morbidity and mortality, with a 30-day mortality rates reaching up to 50%. During the acute phase, major factors contributing to this poor prognosis are hematoma size,1 hematoma expansion,2 and additional intraventricular hemorrhage.3 After the acute phase, neurological deterioration is mainly attributed to the evolution of perihemorrhagic edema with mass effect and increasing intracranial pressure (ICP).4 Although only a few studies have investigated the course of edema evolution, it seems that there is a strong increase during the first week and a peak in the second week after initial bleeding.5

To date, no medical or surgical therapy for ICH and perihemorrhagic edema has been shown to improve outcome after ICH.6 With respect to antiedema therapy, mannitol is still assumed to be the mainstay of hypervosmolar therapy, although there is no study that proved beneficial effect of mannitol on functional outcome after supratentorial ICH.7

Hypertonic saline (HS) solutions have been introduced as a promising alternative for treatment of cerebral edema8 and are now increasingly being used for treatment of traumatic brain injury or brain ischemia, mainly as repeated application of boluses.9 However, optimal dosage and concentration of HS, as well as timing and application schedule, are still unknown. In recent studies, continuous application of HS was investigated in patients with traumatic brain injury10 or acute liver failure11 and positive effects on ICP-lowering properties were reported. Furthermore, no major side effects were observed in critically ill patients with severe stroke or traumatic brain injury treated with continuous 3% HS infusion.12

In patients with severe ICH who are at high risk for development of space-occupying brain edema, it may be beneficial to start an early continuous hyperosmolar infusion to reach a prompt and persisting osmotic gradient, thereby possibly attenuating perihemorrhagic edema evolution. The purpose of this study was to retrospectively investigate the ramification of continuous HS infusion on the development of brain edema after severe supratentorial ICH with hematoma size >30 mL.
Patients and Methods

Selection of Patients

The protocol of this study was approved by the local ethics committee. From May 2008 to December 2009, all patients with severe spontaneous supratentorial ICH >30 mL were included. ICH was defined as spontaneous when no other cause than arterial hypertension or amyloid angiopathy was found. Further inclusion criteria were Glasgow coma scale score <9 at admission or a rapid worsening in neurological status with the necessity of mechanical ventilation and the need for ICP monitoring. Exclusion criteria were age younger than 18 years, surgical hematoma evacuation, infratentorial ICH, pregnancy, and radiological signs of brain herniation at admission, or patients with “do not resuscitate” orders.

Patients of the control group were identified from our prospectively organized ICH database (starting 2006; n=412). To minimize matching bias, inclusion criteria were only supratentorial ICH with a hematoma size on the cranial CT at admission of >30 mL and no decision on admission to stop further medical treatment. According to the HS group, patients receiving surgical hematoma evacuation were excluded. Of a total of 412 patients, 278 were excluded because of hematoma size <30 mL. From the remaining 134 patients, 9 patients were excluded because of infratentorial hemorrhage and 12 patients were excluded because of surgical hematoma evacuation. In a last step, 49 of the remaining 113 patients with the early order for limitation of care were excluded. Hence, 64 patients remained in the control group and received the same standard intensive care management, except for the HS infusion.

Study Protocol for HS Infusion

The hypertonic saline infusion (3%; pharmacy of the University Hospital of Erlangen) was started within 72 hours after symptom onset at the rate of 12 mL/h. Plasma sodium and osmolality levels were controlled at least every 4 hours and the infusion rate was adjusted until the targeted plasma sodium level of 145 to 155 mmol/L and a serum osmolality of 310 to 320 mOsm/kg were reached. Serum osmolality was specified using cryoscopic osmometry measurements. In the first 24 hours of infusion, plasma sodium levels were increased by a maximum of 10 mmol/L. HS infusion was continued until control CT showed a reduction of edema and mass effect compared to previous imaging with midline shift <3 mm, until absence of clinical signs of intracranial hypertension (anisocoria or new reduction of consciousness), and until ICP remained constantly <15 mm Hg for >24 hours. Elevated sodium levels were then decreased by <5 mmol/L daily within a period of 48 hours, with a targeted normonatremia of 135 to 145 mmol/L.

General intensive care management including the maintenance of normoglycemia, normothermia, normovolemia, and an arterial oxygenation >75 mm Hg was ensured. Midazolam was used for sedation and sufentanil was used for analgesia. If necessary, then crystalloidal fluids and norepinephrine were used to keep mean arterial pressure >65 mm Hg and cerebral perfusion pressure >70 mm Hg. Systolic blood pressure was kept between 120 and 160 mm Hg.

All patients including the historical control group received continuous ICP monitoring via external ventricular drainage or parenchymal probe placed in the frontal lobe of the affected hemisphere. An ICP crisis was defined as an ICP >20 mm Hg for ≥20 minutes without noxious stimulation or new anisocoria. If ICP crisis was present, then the patients were treated according to common guidelines18 with repeated boluses of 125 to 250 mL of 20% mannitol, neuromuscular blockade with Cisatracurium, and deep sedation and analgesia.

Data Collection

Predefined primary outcome measures were the course of plasma sodium and osmolality, and adverse effects theoretically associated with HS infusion including cardiac arrhythmia, electrolyte imbalance, acute heart, liver, or renal failure, lung edema, coagulopathy, central pontine myelinolysis, infections, and mortality. Therefore, international normalized ratio, partial thromboplastin time, troponin I, creatinine, urea, lipase, and transaminases were examined every day, and an ECG was performed every second day. Temperature, urine output, central venous pressure, and blood gas analysis including arterial oxygenation, plasma sodium, potassium, osmolality, glucose, and pH were documented every 4 hours as a part of routine intensive care unit management.

Prespecified second outcome measures include the frequency of ICP crises (total number of ICP crises, number of patients with at least 1 ICP crisis, and the ratio of ICP crises per patient), and perihemorrhagic edema evolution using semiautomatic CT volumetry. To get first insights into efficacy of early continuous HS infusion, the outcome measures were compared to those of the historical control group with standard intensive care management.

Imaging Management

Cranial CT was routinely performed on admission (day 1) and day 2, and then based on the clinical course, and before discharge from the intensive care unit. Because time points of CT acquisition during the observational period were not identical among patients, the following time periods were defined for comparison of temporal edema evolution between groups: day 1, day 2, day 3, day 5±1, day 8±1, day 11±1, and day 14±1. For the analysis of edema evolution, only patients with at least 4 CT scans were included.

All CT scans were performed on a fourth-generation Scanner Siemens Somatom using the same protocol. Each CT scan consisted of 10 to 12 slices of 4.8-mm thickness for the skull base and 10 to 12 slices of 7.2-mm thickness for the cerebrum.

Semiautomatic CT Volumetry

Measurement of hematoma and edema volumes was performed using the Siemens Leonardo V semiautomatic software for volumetry. For this purpose, a region of interest was set by generously tracing the hemorrhage including the perifocal hypodense area on each slice. The software then reconstructed a 3-dimensional data set and added up all voxels within a threshold range between 5 and 33 Hounsfield units for perifocal edema and between 44 and 100 Hounsfield units for blood (Figure 1). Measurements were performed by 1 observer (LW) blinded to group allocation and timing of the CT scan. The absolute edema volume (AEV) and the volume of hematoma returned by the software were recorded for each time point. Relative edema volume was calculated as a unitless ratio by dividing AEV by initial hematoma volume.

Statistical Analysis

Statistical tests were performed with the SPSS 16.0 software package (www.spss.com). Data are given in mean±standard deviation, if not indicated differently. All data, including relative edema values at all time points, were distributed normally. The 2-tailed t test was used for single comparisons of relative edema values and AEV values between the 2 groups. A multifactorial ANOVA (general linear model for variance analysis) was performed for between-group comparison of the time course of relative edema in the HS treatment group and control group. Frequency distributions were analyzed using the Fisher exact and χ² tests. P<0.05 was considered significant.

Results

Characteristics of Patients

Twenty-six patients were enrolled in the HS group and 64 patients were enrolled in the control group. As shown in Table 1, the 2 groups were comparable for age, gender, initial Glasgow coma scale score, hematoma size, and location of ICH. In both groups, all patients were sedated and mechanically ventilated. All patients included in the HS group and all patients identified for the historical control group underwent at least 4 CT scans.
Median time until HS infusion was started was 12 hours (3–69 hours) and median duration of HS infusion was 12 days (minimum, 4 days; maximum, 20 days), with a mean infusion rate of 0.36–0.17 mL/kg/h (range, 0.16–0.57 mL/kg/h). As shown in Figure 2, at baseline (day 1), plasma sodium levels and osmolality were comparable between the groups. However, at days 3 to 14, there was a significant difference between the groups for both the sodium concentration and osmolality ($P<0.001$). The target plasma sodium level (145 to 155 mmol/L) was reached on average at day 3, and target osmolality was reached on average at day 4.

### Effects of HS on Edema Evolution

#### Absolute Edema Volume

AEV on admission was comparable between the 2 groups ($P=0.33$; Figure 3). In the HS group, the AEV increased slowly from day 3 until day 14 (within-group comparison, ANOVA, $P=0.114$; $F=2.622$). In contrast, in the control group, edema increased continuously over the observational period, and the within-group comparison (ANOVA) showed a significant difference between AEV at admission and all following time points ($P=0.047$; $F=2.622$). After 8 days, AEV had increased by 50% as compared to the edema volume on admission, and by 72% after 14 days. In contrast, in the HS group, AEV at day 14 had increased by only 15%. The between-group comparison of the time course of AEV revealed a significant difference between the HS group and the control group (ANOVA; $F=4.531$; $P=0.04$).

#### Relative Edema Volume

On admission, mean relative edema volume was smaller in the HS group, but the difference was not significant (0.74

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HS Group (n=26)</th>
<th>No HS Group (n=64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean)</td>
<td>63.9</td>
<td>68.1</td>
<td>0.85</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Prehospital Glasgow coma scale score</td>
<td>7 (range 3–9)</td>
<td>8 (range 3–9)</td>
<td></td>
</tr>
<tr>
<td>Hematoma location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>9 (34.6%)</td>
<td>29 (45.3%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Thalamic/basal ganglia</td>
<td>17 (65.4%)</td>
<td>35 (54.7%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

HS indicates hypertonic saline.

Figure 1. Representative computed tomography scans for a patient in the hypertonic saline group (A) and in the control group (B) at days 3, 8, and 11. The pink line surrounds the region of interest for volume calculation. The pink area represents perihemorrhagic edema on a threshold basis algorithm.
versus 0.98; \( P=0.14 \); Figure 4). However, between day 2 and day 14, mean relative edema volume of the HS group was significantly lower compared to that of the control group at each day. The between-group comparison (ANOVA) during time course showed a significant reduction of relative edema volume in the HS group (\( P=0.021; F=5.818 \)).

**Effects of HS on ICP Crisis and In-Hospital Mortality**
An ICP crisis (>20 mm Hg for >20 minutes; new anisocoria) was observed in 9 (34.5%) of 26 patients in the HS group and in 32 (50%) of 64 patients in the control group (\( P=0.092 \)). Total number of ICP crisis was 12 in the HS group and 56 in the control group (\( P=0.048 \)). Thus, mean number of ICP crises per patient was 1.33 versus 1.75 (\( P=0.09 \)).

In-hospital mortality was 3 of 26 patients (11.5%) in the HS treatment group and 16 of 64 patients (25%; \( P=0.078 \)) in the control group. The cause of in-hospital death in all deceased patients was progression of midline shift with consecutive transtentorial and transforaminal herniation.

**Side Effects of HS**
The frequency of complications theoretically linked to HS therapy is shown in Table 2. Periods of severe hypernatremia (>159 mmol/L) were observed in 6 (23.2%) patients in the HS group and in no patients in the control group. New cardiac arrhythmia, acute heart failure, or cases of acute coronary syndrome (rapid troponin I increase with or without ST elevation or decline in ECG) were recorded to a similar extent in both groups, as were lung edema, acute liver failure, sepsis, or relevant coagulopathy. Cases of acute renal failure (creatinine >20 mg/L or glomerular filtration rate <20 mL/min or oliguria) were observed in 2 (7.69%) patients in the HS group and 5 (7.81%) patients in the control group (\( P=0.99 \)). Cases of central pontine myelinolysis were not observed in any group.

**Discussion**
In this study we report about the effects of early and continuous hypertonic saline solution (3%) in patients with large spontaneous supratentorial hemorrhage. The application
regimen we used was chosen for several reasons. The targeted plasma sodium levels (145–155 mmol/L) with an estimated target osmolality of 310 to 320 mOsmol/kg were selected because a robust antiedema effect without major side effects has been reported for these ranges in previous studies.\textsuperscript{11} Theoretically, an early start of osmotherapy before critically elevated ICP occurs appears more reasonable and continuous application of HS to maintain a stable and persistent osmotic gradient may have advantages as compared to repeated bolus application. An early induced and persistent osmotic gradient may attenuate the progression of cerebral edema and finally reduce the frequency and severity of episodes with critical intracranial hypertension. Because the exact duration of edema progression is still unknown, we continued HS infusion until ICP remained stable at normal values, until brain imaging showed a reduction of edema, and until the absence of clinical signs of intracranial hypertension, ie, anisocoria or reduction of consciousness.

The target values for sodium of 145 to 155 mmol/L and osmolality of 310 to 320 mOsmol/kg were feasible and safe in patients with large ICH. Neurological complications that have been reported in association with HS infusion, including seizures, central pontine myelinolysis, and rebound phenomenon, were not observed in our patients. We did not notice signs of neurological worsening that could be clearly attributed to HS infusion. Particularly, no patients in the HS group had clinical or radiological signs of central pontine myelinolysis, and no rebound increase of ICP during tapering of HS therapy was observed. Certainly, in our patients with severe ICH, clinical side effects potentially linked to HS infusion were not easy to detect because clinical monitoring is limited in sedated and ventilated patients and neurological deterioration can be part of the natural course in neurocritically ill patients.

Several systemic complications of HS infusion have been mentioned in the literature, including renal dysfunction, intravascular volume overload with subsequent cardiac insufficiency, coagulopathy, higher infection rates, and electrolyte imbalance with hypocalcemia and hyperchloremic acidosis.\textsuperscript{14–16} We did not observe an increased incidence of any of these complications, and none of the analyzed parameters showed evidence for HS-associated complications as compared to the control group. Our findings are in accordance with those of a recently published study analyzing potential complications of continuous HS infusion in neurocritically ill patients.\textsuperscript{17} This is not surprising because most studies of hypertonic saline solutions did not report safety concerns with sodium values up to 160 mmol/L and osmolality values up to 320 mOsm/kg.\textsuperscript{10,18} Thus, based on previous studies and the findings of the present study, continuous infusion of 3% HS with target ranges of sodium of 145 to 155 mmol/L and of osmolality of 310 to 320 mOsm/kg with a maximum daily

### Table 2. Frequency of Complications

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HS Group (n=26)</th>
<th>No HS Group (n=64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cardiac arrhythmia</td>
<td>3 (11.54%)</td>
<td>8 (12.5%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Increase of troponin I</td>
<td>3 (11.54%)</td>
<td>8 (12.5%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>3 (11.54%)</td>
<td>9 (14.1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>1 (3.85%)</td>
<td>2 (3.125%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2 (7.69%)</td>
<td>5 (7.81%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Lung edema</td>
<td>2 (7.69%)</td>
<td>4 (6.25%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>6 (23.1%)</td>
<td>8 (12.5%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Central pontine myelinolysis</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia (&lt;135 mmol/L)</td>
<td>5 (19.23%)</td>
<td>29 (45.31%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Hypermotremia (&gt;159 mmol/L)</td>
<td>6 (23.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CSWS</td>
<td>2 (7.69%)</td>
<td>1 (1.56%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 (30.77%)</td>
<td>10 (15.625%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

CSWS indicates cerebral salt wasting syndrome; HS, hypertonic saline.
sodium increase <10 mmol/L seem to be safe in patients with severe supratentorial ICH.

The target values for sodium and osmolality were chosen based on previous reports of efficacy and safety. However, the questions whether these thresholds represent the optimal range for a safe and effective antiedema therapy and whether an earlier start of HS, a faster increase of plasma sodium, and a higher sodium concentration may be more beneficial were beyond the scope of this study and remain to be further investigated.

Beside the safety aspects, we tried to get first insights in potentially beneficial effects of early continuous HS infusion on ICP control and mortality by comparing our results to those of a historical control group. With respect to this control group and the findings of previous studies, we observed a less robust edema progression than we might have expected in patients receiving HS infusion.

This finding may be of significance. Although the mass effect of the initial hematoma is the major determinant for high morbidity in the acute phase of supratentorial ICH, the progressive evolution of perihemorrhagic edema represents the main factor for clinical deterioration in the subacute phase, and the growth of edema is strongly related to the size of underlying hematoma in supratentorial ICH. Thus, in the present study, only patients with large hematoma (>30 mL) were included because these patients were likely expected to have critical extent of perihemorrhagic edema in the course of the disease.

In the HS group, total number of ICP crises and in-hospital-mortality were reduced when compared to the historical control group. However, the number of patients with ICP crisis was not significantly different between groups (P=0.092). This might be explained, at least in part, by the relatively small sample size and reduced statistical power. Moreover, patients in the HS group with ICP crisis usually had only 1 episode (6 of 9 patients), whereas the majority of patients in the control group when experiencing ICP crisis had >1 episode (27 of 32 patients). Note, patients in the HS group were younger and had smaller AEV and relative edema volumes at baseline. Although these differences were not statistically significant, we cannot exclude that these factors may have influenced the course of edema, the frequency of ICP crises, and mortality.

Certainly, this study has several limitations, mainly because of the comparison to a historical control group and the relatively small patient number. Using a historical control group has clear limitations with particular risk of bias and does not allow definite interpretation and generalization of the observed data. Moreover, long-term functional outcome was not investigated. However, the study was a pilot study to evaluate a new treatment approach in severe ICH patients. Thus, it was designed as a feasibility and safety trial and not as a controlled randomized study to investigate effect on outcome.

In conclusion, early and continuous infusion of 3% HS was feasible in patients with severe supratentorial ICH without evidence of major side effects. The impact of this treatment approach on perihemorrhagic edema evolution and functional outcome has to be investigated in a randomized trial.

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Disclosures
None.

References
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혈종주위 부종의 발달에 대한 고장식염수 지속 주입의 효과

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(Stroke. 2011;42:1540-1545.)

Key Words: hypertonic saline ■ intracerebral hemorrhage ■ perihemorrhagic edema

배경과 목적
혈종의 증괴효과(mass effect)와, 이와 관련된 혈종주위 부종(perihematomatol edema)은 뇌내출혈(intracerebral hemorrhage) 이후 심정한 합병증을 설명하는 주된 요인이다. 수술적 치료와 약물 치료의 효과는 제한적이다. 저자들은 심한 자발성 전막상 출혈(severe spontaneous supratentorial hemorrhage) 이후 혈종주위 부종의 발생에 대한 고장식염수(hypertonic saline)의 조기 지속 주입 효과에 대하여 연구하였다.

방법
30 mL가 넘는 자발성 업뇌(lobar) 및 기저핵/시상 출혈 환자(n=26)를 대상으로 조기(72시간 이내)에 고장식염수(3%)를 지속 주입하여 145~155 mmol/L의 나트륨 및 310~320 mOsmol/kg의 오스모 농도(osmolality)에 도달하도록 치료하였다. 질병 주변 부종과 상대 부종 부피(절대 부종 부피/조기 혈종 부피의 비율)가 가장 큰 것을 두 개 CT를 반복 시행하여 평가하고, 데이터베이스에서 혈종이 30 mL가 넘는 것을 확인한 이전 환자(n=64)와 비교하였다.

결과
치료군에서 조기 주입군의 8~14일에 유의하게 작았고, \( P_{\text{absolute edema volume}} = 0.04 \) 상대 부종 부피는 2~14일에 유의하게 작았다고 \( P_{\text{relative edema volume}} = 0.02 \). 두개내압 위기(20분 이상 20 mm Hg가 넘거나 세로운 동공부등(anisocoria)이 발생)은 치료군에서 적게 발생하였습니다(12 vs. 56; \( P = 0.048 \)). 뇌혈관 내 사망은 고장식염수 치료군에서 3명(11.5%)이었고 대조군에서 16명(25%)이었다(\( P = 0.078 \). 이론적으로 고장식염수와 관련된 부작용인 심장부전, 급성 심부전, 심부전은 두 군에서 비슷하게 발생하였다.

결론
증상의 자발성 뇌내출혈 환자에서 조기 고장식염수 지속 주입은 시행할 만하다고 안전하였다. 부종 발달과 결과에 대한 이러한 치료법의 유익한 효과가 대조 연구를 통하여 입증되었다.