2014

Is 30 mL Cerebrolysin a Safe and Effective Drug for Improving Global and Cognitive Function in Patients with Alzheimer's Disease Aged 50 Years and Older with No Significant Comorbidities?

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Is 30 mL Cerebrolysin a safe and effective drug for improving global and cognitive function in patients with Alzheimer’s disease aged 50 years and older with no significant comorbidities?

Anthony Champion PA-S
A SELECTIVE EVIDENCE BASED MEDICINE REVIEW
In partial Fulfillment of the Requirements For
The Degree of Master of Science
In
Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013
ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of 30 mL Cerebrolysin is a safe and effective drug for improving global and cognitive function in patients with Alzheimer’s Disease aged 50 years and older with no significant comorbidities.

STUDY DESIGN: Systematic review of three randomized controlled trials published between 2001-2006, all English language.

DATA SOURCES: Three randomized controlled trials comparing the efficacy of cerebrolysin to placebo in the treatment of individuals ages 50 and over with AD related cognitive and global functioning decline. All articles found using PubMed.

OUTCOMES MEASURED: Three randomized controlled studies measured improvement in cognitive and global impairment in patients with AD using a combination of either ADAS-cog (clinician rated test measuring cognitive function), CIBIC+ (clinician based interview of patient to assess global change), or CGI (clinician assessment of mental deterioration). The evaluations cover orientation, memory, language, understanding, behavior, and activities of daily living. Evaluations with the tests mentioned were made under double-blind conditions.

RESULTS: Three randomized controlled trials were included in this review. Ruether et al. revealed a significant effect on functional and cognitive decline with 30mL Cerebrolysin. Panisset et al. found a significant relationship between Cerebrolysin and improved global functioning, but no change in cognition between experimental and control groups. Alverez et al. found insignificant effects on both cognition and global functioning.

CONCLUSIONS: The results of the three studies represent inconclusive evidence that Cerebrolysin has significant effects on cognition and global functions in patients with AD. One study found significant improvements in cognition and global function, but the other studies found insignificant effects. Further studies are encouraged to develop a definitive relationship.

KEY WORDS: cerebrolysin, alzheimer’s disease, randomized
INTRODUCTION

Alzheimer’s disease (AD) is the most common neurodegenerative disorder. It is characterized by progressive behavioral and cognitive deficits accompanied by diffuse structural abnormalities in the brain. Cerebrolysin, a peptide solution, may have the properties to stabilize neurons and decrease amyloid production to improve cognition and global functioning in patients with AD.

An estimated 10% of patients age 70 years and older have significant memory loss, and over half of that population contribute the memory loss to AD. It is the most common cause of dementia in the elderly and the sixth leading cause of death in the US. There are around 125 new cases per 100,000 people annually for ages 60 and over and around 3,200 new cases per 100,000 for those 70 to 79. An estimated 5.2 million Americans have AD in 2013. As the number of Americans surviving into 80s and beyond continues to grow, and the baby boomer generation ages, it can be assumed Alzheimer’s disease will become even more prevalent in the future.

The estimate costs to care for an elderly patient with AD for one year are around $50,000. Furthermore, the US as a whole spends close to $100 billion annually to care for patients with AD. A large burden is also placed on unpaid caregivers who provided an estimated 17.5 billion hours of unpaid care in 2012, valued at more than $216 billion. The annual drug cost for Cerebrolysin has not been identified. In 2008, 349 patients required stays in skilled nursing facilities per 1,000 Medicare beneficiaries with Alzheimer’s and other dementias. Also, there were 780 hospital stays per 1,000 Medicare beneficiaries for those age 65 and older with AD or other dementias.

AD Pathology hallmarks include amyloid plaques, neurofibrillary tangles, and diffuse loss of neurons and synapses. Neuronal and synapse loss primarily in the subcortical regions of
the brain. It is known that amyloid is toxic to neurons and synapses but the pathophysiology is not completely understood. There is loss of cortical proteins and neurotransmitters like acetylcholine and nicotinic cholinergic receptors. Also, noradrenergic and serotonergic depletion from further degeneration subcortical brain regions. Symptoms include language impairment, memory loss, agitation, anxiety, memory loss, apraxia, impaired executive function, and sleep disorders.

Due to the complexity of the pathologic process involved in AD the conventional treatments to date focus on symptomatic benefit. Usual methods for treating AD consists of acetylcholinesterase inhibitors which increase levels of Acetylcholine available at the synaptic cleft. Conventional acetylcholinesterase inhibitors include tacrine, donepezil, rivastigmine, and galantamine. NMDA receptor blockers, such as memantine, are used as adjunctive treatment to stabilize cognition and function primarily in moderate and severe disease. Non-traditional treatments include Axona, which provides an alternative fuel source of ketones for brain. Pharmaceuticals such as trazodone, haloperidol, thioridazine, risperidone help behavioral and sleep disorders associated with Alzheimer’s disease. All of the medications available are centered on symptomatic relief and are effective for a limited time. The focus of current drug development aims at stabilization strategies to delay the disease process.

The method of treatment with Cerebrolysin is being proposed because currently there is no cure for Alzheimer’s disease; although the medications above have seemed to temporarily improve symptoms of patients with AD. Cerebrolysin may be used as an IV alternative for the stabilizing the disease process, relief of symptoms associated with AD, and improving activities of daily living. This selective evidence-based medicine review evaluated three double-blind,
randomized controlled trials comparing the efficacy of Cerebrolysin as an IV medication for improving global and cognitive function in patients 50 years and older with AD.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the use of 30 mL Cerebrolysin is a safe and effective drug for improving global and cognitive function in patients with Alzheimer’s Disease aged 50 years and older with no significant comorbidities.

METHODS

The populations criteria used for selection in the studies included men and women age 50 year and older with Alzheimer’s disease. The interventions studied in the RCTs was Cerebrolysin 30 mL IV infusion. Comparisons was made between the treatment group receiving Cerebrolysin to the experimental group who received a visually matched Placebo. Outcomes measured involved the efficacy and tolerability of Cerebrolysin for the treatment of AD, and improvement in cognitive and global functioning. The types of studies included were three randomized, double-blind, placebo controlled clinical trials.

The key words used in the searches were “Alzheimers disease,” “Cerebrolysin,” and “randomized.” All articles were published in peer reviewed journals in the English language. The author searched articles via PubMed and Cochrane library, and articles were selected based on their relevance to the clinical question and inclusion of patient oriented outcomes(global functioning and cognition). Inclusion criteria consisted of studies in which the design was randomized, controlled, double blind, and patient-oriented outcomes(POEMs). Exclusion criteria consisted of studies with patients under 50 years old or non-Alzheimer’s form of dementia. The summary of statistics are reported using relative benefit increase(RBI), absolute benefit increase(ABI), numbers needed to treat(NNT), 95% confidence interval(CI), and p-value.
Table 1 – Demographics & Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age(yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez(^1) (2006)</td>
<td>Double blind RCT</td>
<td>279</td>
<td>50+</td>
<td>diagnosis of AD, mini mental state exam (MMSE) scores from 14-25, Mod. Ischemia scale score ≤4, CT/MRI within 12 months</td>
<td>Pt with any psychiatric disorder, or psychoactive substance dependence; other dementia; brain trauma, other neurologic disease</td>
<td>42</td>
<td>IV infusion of Cere 10mL, 30mL or 60 mL five times a week for 4 weeks and then two times a week for 8 weeks</td>
</tr>
<tr>
<td>Panisset(^2) (2002)</td>
<td>Double blind RCT</td>
<td>195</td>
<td>60+</td>
<td>diagnosis of AD, mini mental state exam (MMSE) from 10-26, Mod. Ischemia scale &lt;5, caregiver regularly present, CT/MRI within 12 months</td>
<td>Pt with any psychiatric disorder, or psychoactive substance dependence; other dementia; brain trauma, other significant illness</td>
<td>16</td>
<td>IV infusion of Cere 30 mL five times a week for 4 weeks</td>
</tr>
<tr>
<td>Ruether(^3) (2001)</td>
<td>Double blind RCT</td>
<td>149</td>
<td>50-85</td>
<td>diagnosis of AD, mini mental state exam (MMSE) from 14-24, Mod. Ischemia scale &lt;5, CT/MRI within 12 months</td>
<td>Pt with any psychiatric disorder, or psychoactive substance dependence; other dementia; brain trauma</td>
<td>8</td>
<td>IV infusion of Cere 30 mL five times a week for 4 weeks, 2 months therapy free, and repeat</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

Three randomized controlled studies measured improvement in cognitive and global impairment in patients with AD using a combination of either ADAS-cog (clinician rated test measuring cognitive function), CIBIC+ (clinician based interview of patient to assess global change), or CGI (clinician assessment of mental deterioration). ADAS-cog evaluations cover orientation, memory, language, and understanding. CIBIC+ and CGI evaluations examine activities of daily living and behavior. All outcomes measured were patient oriented outcomes (POEMs) and evaluations were conduction at baseline and throughout the studies. The clinician evaluated patients through a direct patient interview, and patient caregiver input was used with CIBIC+. Evaluations with the tests mentioned were made under double-blind conditions.

RESULTS

The study conducted by Alvarez et al was a 24 week, double blind, randomized controlled study between Cerebrolysin and a visually matched placebo. In total 65 individuals were randomized and treated with 30 mL Cerebrolysin and 58 with placebo. The Cere group was infused with 30mL Cerebrolysin 5 days a week for 4 weeks, and then 2 days a week for 8 weeks. The placebo group regimen was the same. Post-treatment phase included observing for continued effects from previous treatment. Cognitive effects were based on ADAS-cog scores, measure of cognition through clinician based interview and performance testing that covers memory, orientation language, and comprehension on 70 point scale. Cerebrolysin had no statistically significant effects on cognition with 36.9% of Cerebrolysin patients showing improvement and 24.1% of placebo patients improving (p=.069) as displayed by Table 2. At the study endpoint overall the patients in Cerebrolysin group performed better in cognitive testing than baseline, while patients on placebo had deteriorated by about 2 points in ADAS-cog
evaluations. Global functioning outcomes in this study were measured through an evaluation with CIBIC+, which correlates behavior and activities of daily living. 60% of the patients treated with 30 mL Cerebrolysin experienced an improvement in global functioning while only 20.7% of placebo patients improved (Table 3). The most common adverse effects recorded throughout the study were UTI and depression. 50.7% of subjects in the Cerebrolysin treatment group experienced at least one AE, while 60% of placebo subjects recorded one AE (Table 3). 2 subjects in the Cerebrolysin group experienced serious AEs. Only one of the serious AEs proved a causal relationship in which the patient developed bacteremia from IV administration.

Table 2: Increase in cognitive functioning in patients treated with 30 mL Cere compared to placebo

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Numbers needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.1%</td>
<td>36.9%</td>
<td>.5%</td>
<td>12.8%</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3: Increase in global function in patients treated with 30mL Cere compared to placebo

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Numbers needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.7%</td>
<td>60%</td>
<td>1.89%</td>
<td>39.3%</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4: Total adverse events recorded during Alvarez et al study

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative risk increase (RRI)</th>
<th>Absolute risk increase (ARI)</th>
<th>Numbers needed to harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60%</td>
<td>50.7%</td>
<td>-.016%</td>
<td>-9.3%</td>
<td>-10</td>
</tr>
</tbody>
</table>

Ruether et al. conducted a 28 week, double blind, randomized controlled study between Cerebrolysin and a visually matched placebo. In total 76 individuals were randomized and treated with 30 mL Cerebrolysin and 70 with placebo. The groups were infused with 30mL Cerebrolysin 5 days a week for 4 weeks, a 2 month treatment free interval, and repeated the same regimen. The placebo group matched this regimen using normal saline. After the treatment
Champion, Cerebrolysin and Alzheimer’s, 9

Phase patients were followed for continued effects. The mean difference in CGI, on an 8 point scale, between Cerebrolysin and placebo was .42 in favor of Cere. Patients with CGI score less than 5 were considered to have a positive global response to therapy. At the end of the study, 45.9% of Cere treated patients showed a positive global response compared to 28.6% in the placebo group. The cognitive domain, measured using ADAS-cog, proved significant effects by Cerebrolysin. At the end of the active treatment phase a significant treatment effect was shown with 43.7% of Cere patients compared to 15.7% of placebo patients showing improvement. At 28 weeks placebo pts scores had deteriorated by a mean of 1.6 points in the ADAS-cog, and patients on Cere maintained baseline, p=.016. Correlation between global and cognitive improvements were seen in 57.4% Cere treated patients and 27.5% of placebo patients with a p of .006 and 95% CI of -.12/-0.72(table 5). Incidence of adverse effects was similar in both groups with 43.4% in Cere group and 38.0% in placebo group have atleast one AE(Table 6). The most common adverse effects were vertigo, headache, increased sweating, and nausea. Cere caused no significant changes in vital signs and no deaths in this study. The absolute risk increase was 5% with most adverse events being mild(38.2%) and similar severe AEs rates in both groups; 1.2% less severe AEs in favor of Cerebrolysin.

Table 5: Correlated increase in global functioning and cognitive ability with treatment of Cere compared to placebo

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Numbers needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.5%</td>
<td>57.4%</td>
<td>1.09%</td>
<td>29.9%</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 6: Total adverse events recorded during the study

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative risk increase (RRI)</th>
<th>Absolute risk increase (ARI)</th>
<th>Numbers needed to harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>43.4%</td>
<td>.014%</td>
<td>5.4%</td>
<td>19</td>
</tr>
</tbody>
</table>
Panisset et al conducted a 24 week, double blind, randomized controlled study between Cerebrolysin and a visually matched placebo. In total 95 patients were randomized and treated with Cerebrolysin, and 94 patients treated with placebo. The groups were infused with either 30mL Cerebrolysin or placebo on 5 days a week for 4 weeks. Following the active treatment phase the patients were observed to determine long term efficacy. The scope of global functioning was measured using CIBIC+, a clinician based interview assessing cognitive state, behavior, and activities of daily living on a scale of 0(marked improvement)-7(marked deterioration). Mean change in CIBIC+ at the end of active treatment 3.82 ± .09 for placebo and 3.88 ± .07 for Cerebrolysin. At Week 12, two months following end of treatment, patients whom received Cerebrolysin had a mean difference of -.21 points on CIBIC+ in favor of Cere (95% CI=-.5-.08, p=.033). Week 12 revealed global improvement in 76% of treated patients compared to 57% in patients on placebo, as shown in table 7. At the end of the study the mean change in CIBIC+ was 4.46 ± .12 for placebo and 4.42 ± .12 for Cerebrolysin, which are not statistically significant effects at 6 months. By the end of the study the mean difference in CIBIC+ was .4 between the groups. The cognitive effects of Cerebrolysin were measured using evaluation with ADAS-cog. Cognitive effects were minimal and insignificant at all points in the study. The ADAS-cog mean score at week 12, 2 months after active treatment, was -.88 ± .61 for placebo and .04 ± .64 for Cere, p value = .284. At the end of treatment ADAS-cog mean difference was 1.81 points. The incidence of atleast one adverse event was 64% in Cerebrolysin patients and 73% in placebo patients. No change in vital signs were observed with the use of Cere and 1 death occurred ten weeks after last infusion due to pneumonia. The most common AEs in patients on Cere were headache(13%) and dizziness(8%), and placebo had similar rates at 11% and 12% respectively.
Table 7: Increase in global functioning in patients treated with 30 mL Cere compared to placebo

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative benefit increase (RBI)</th>
<th>Absolute benefit increase (ABI)</th>
<th>Numbers needed to treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>76%</td>
<td>0.33%</td>
<td>19%</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 8: Total adverse events recorded during the study

<table>
<thead>
<tr>
<th>Control event rate (CER)</th>
<th>Experimental event rate (EER)</th>
<th>Relative risk increase (RRI)</th>
<th>Absolute risk increase (ARI)</th>
<th>Numbers needed to treat (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73%</td>
<td>64%</td>
<td>-.12%</td>
<td>-9%</td>
<td>-11</td>
</tr>
</tbody>
</table>

DISCUSSION

The studies covered in this review covered Cerebrolysin as a possible treatment to stop and potentially reverse the pathologic process of AD. All studies performed and evaluated in this review were controlled, double blind research over a significant period of time with reputable evaluation measures.

The studies were limited by the insufficient evidence suggesting appropriate Cerebrolysin treatment frequency and schedule. Patients between each of the three studies were subject to different treatment schedules. Ruether et al treated patients for 8 weeks, Alvarez et al. for 12 weeks, and Panisseta et al for 4 weeks. None of the studies administered Cerebrolysin at the same frequency throughout their respective study. Alvarez, Ruether, and Panisset et al. studied populations of 123, 146, and 183 respectively. Each sample size was significantly large, diverse, and studied over 6-7 month intervals.

Cerebrolysin is a peptide preparation with neurotrophic activity. It mimics the effects of endogenous neurotrophic factors. Neurotrophic factors regulated nervous tissue functions in a healthy environment. Natural NTFs cannot cross BBB due to complex three-dimensional
complexion, but the active ingredient in Cerebrolysin, neuropeptides, can. Cerebrolysin induces neuronal sprouting, neurogenesis, and neuroplasticity. The concern with this medication is that it is extracted from pig brain and all of its components are not completely understood. It is not currently FDA approved for the use of Alzheimer’s disease in the US although it is used in other numerous other countries. The availability of Cerebrolysin is a concern if it progresses to become a widely used commercial product because it is not a synthetic product. The administration of Cerebrolysin is via IV infusion, which is another concern towards its accessibility, long term use, and insurance coverage.

CONCLUSIONS

The evidence for Cerebrolysin as an effective treatment for AD is inconclusive. The efficacy of Cerebrolysin was contradictory in the three studies analyzed in this review. The effects on ADLs and behavior, measured by CIBIC+ and CGI, were significant in studies performed by Ruether et al. and Panisset et al. The study performed by Alvarez et al. found borderline but insignificant effects on ADLs and behavior with a p-value of .069 and wide 95% CI. Evidence for improvement in cognitive function with use of Cerebrolysin in AD is also contradictory. Studies by Alvarez et al. and Panisset et al. found insignificant effects on cognitive functioning, measured by ADAS-cog, but Ruether et al. found significant improvement in cognitive functioning. Further studies are encouraged to clarify the efficacy of Cerebrolysin in AD.

The treatment regimen for all three studies was significantly different and offers an area to focus improvement. The Ruether et al. study is the only study that found global and cognitive improvements and incorporated a regimen of 5 days a week for 4 weeks, a 2 month treatment free interval, and then another 5 weeks of treatment. Using a treatment plan that has proven to be effective may solidify the effects of Cerebrolysin on AD patients. There have been several
other studies performed, with the most recent in 2012. In the design of future studies the all screening parameters used in these studies would be efficient in selecting an unbiased patient population, using the treatment regimen stated above, and exploring the influences of increased frequency of Cerebrolysin administration.
References


