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Perindopril and residual chronic subdural hematoma volumes six weeks after burr hole surgery: A randomized trial☆

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ABSTRACT

Objective: Recurrence rates of between 5% and 25% have been reported following surgery for chronic subdural hematoma (CSH). A previous study showed that the treatment with angiotensin converting enzyme (ACE) inhibitors decreases the risk of recurrence. To test the effects of ACE inhibitors on the recurrence CSH and CSH remnant six weeks after surgery, we conducted a prospective double-blinded randomized controlled clinical trial on patients with CSHs from July 2009 until October 2012.
Patients and methods: Patients eligible for burr hole surgery for CSH were randomized into either an ACE inhibitor perindopril 5 mg or placebo treatment daily for three months prior to surgery. Cerebral CT scans were performed after six weeks, and clinical follow-ups were performed three months after surgery. Additionally, a retrospective analysis of the data and CT scans from all nonrandomized patients from the same time period was performed.
Results: Forty-seven patients were included in the randomized study. The patients' preoperative Glasgow Coma Scale scores were 15. None of the patients in the randomized group developed a recurrence after surgery. Measurements of the sizes of the CSH before and six weeks after surgery revealed no difference between the placebo and perindopril-treated groups. In the retrospective group (245 patients), there was no correlation between the risk of recurrence and ACE inhibitor treatment.
Conclusion: Our data suggest that perindopril does not diminish the size of residual CSHs six weeks after burr hole surgery and that ACE inhibitors do not decrease the risk of CSH recurrence.
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1. Introduction

Chronic subdural hematomas (CSHs) are common acute and sub-acute neurosurgical conditions [1–4].

It has been hypothesized that the breakdown products of the blood on the surface of the brain result in osmotically active substances retracting liquid from the bloodstream into the CSH. This process would result in a gradual increase in the size of the CSH and the development of clinical symptoms. However, this hypothesis has been questioned as the only explanation for the development of CSH based on measurements of the osmolality of CSH fluid [5].

Other studies have focused on the outer membrane (neomembrane) and its immature and leaky blood vessels. Analyses of the hematoma fluid and the neomembrane have revealed several angiogenesis-promoting factors including vascular endothelial growth factor (VEGF). Although the cellular origin of these growth factors has not been established [5–12], the presence of VEGF in hematoma fluid has been suggested to induce angiogenesis of immature and leaky blood vessels in the neomembrane and thereby promote the growth and recurrence of CSHs.

Symptomatic CSHs are treated surgically. Typically, a burr hole with dural and underlying neomembrane opening followed by thorough rinsing and closed subperiosteal [13] or subdural drainage is employed [14]. In cases of CSHs with several membranes present on cerebral computed tomography scans (CTCs), a craniotomy may be needed.

Regardless of surgical method, the risk of recurrence has been reported to be as high as 25% [3,15].

Angiotensin converting enzyme (ACE) inhibitors are well-established pharmaceutical compounds that are used in the

Abbreviations: CSH, chronic subdural hematoma; ACE, angiotensin converting enzyme; CTC, cerebral computed tomography scan; MAP, mean arterial blood pressure; GCS, Glasgow Coma Scale; VEGF, vascular endothelial growth factor; MRC, magnetic resonance imaging; INR, international normalized ratio.

☆ Industry affiliation: This project has no affiliations with industry.

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treatment of arterial hypertension, and ACE inhibitors have been shown to inhibit the development of new blood vessels in the retinae of diabetic patients [16–18]. A combined prospective and retrospective study showed that patients treated with ACE inhibitors are at a reduced risk of developing CSHs regardless of dose used or the use of generic compounds; furthermore, in those patients who developed a CSH, the risk of recurrence was reduced from 18% to 5% [6]. Although the mechanism is unknown, it has been proposed that ACE inhibitors can reduce the development of new and immature blood vessels in the neomembrane via reducing the production of VEGF [6], which reduces the extravasation of fluid into the CSH.

The present prospective and double-blinded randomized controlled study and combined retrospective analysis of patients who were not randomized was designed to investigate whether treatment with the ACE inhibitor perindopril could reduce the risk of recurrence and/or the amount of residual CSH fluid present on CTCs that were scheduled six weeks after burr hole treatment for CSH.

2. Methods

This study was approved by the Danish Health Research Ethics Committee, the Danish Health and Medicines Authority and the Danish Data Protection Agency and was conducted in accordance with Good Clinical Practice. This study included all patients admitted to the Department of Neurosurgery of Odense University Hospital, which is a medium-sized neurosurgical department in Denmark (single center), from July 2009 until October 2012 (i.e., the follow-up of the last randomized patient).

The data were evaluated after the inclusion of 47 patients (i.e., randomization ID 50 of the 100 patients who were intended for inclusion).

2.1. Randomization and masking

Patients with a CTC – or cerebral magnetic resonance imaging (MRC) – verified CSH and symptoms that required surgery were eligible for inclusion. The inclusion criteria were as follows: patients with a CSH, an indication for burr hole surgery, and a minimum of 18 years of age. The indication for surgery was the following: headache, nausea, vomiting and neurological deficits such as hemiparesis, aphasia or cognitive changes. The exclusion criteria were a lack of ability to comply due to such factors as impaired consciousness, renal artery or aorta stenosis, impaired renal function, allergies or intolerance of ACE inhibitors, coagulopathy, malignant disease, fertile women, severe neurological disorders and treatment with drugs that contraindicated treatment with ACE inhibitors. For the diabetic patients, blood glucose levels were measured four times daily for the first three days after randomization. Upon admittance, informed consent was obtained, and the patients were double-blindly randomized to 90 days of oral treatment with either placebo or 5 mg perindopril (Coversyl®, Servier, Denmark) ingested daily in the morning. Both the placebo and perindopril tablets were individually wrapped in small lactose containers that were easy to swallow, which made it impossible to distinguish the placebo from the active compound. Background information, including age, gender, history of head trauma, anticoagulation therapy, blood pressure, heart rate, Glasgow Coma Scale (GCS) score, neurological deficits, headache, nausea/vomiting and the size of the CSH, were collected. The randomized patients received a diary in which they noted each day the medicine was ingested. Possible side effects were noted.

Blood sample analyses, including measurements of blood potassium, sodium, creatinine and urea, were performed.

Based on published data from Weigel et al. [6], a sample size of 100 patients was determined (significance level 0.05, power 0.8). A planned interim analysis of the data following the inclusion of half of the intended patient population was performed.

2.1.1. Trial registration information

This study is registered at www.clinicaltrials.org under the title, “Chronic subdural hematoma – reduction of recurrence by treatment with Angiotensin Converting Enzyme Inhibitors”, and at the European Medicines Agency (EMEA) under EudraCT number 2009-010058-37.

2.2. Surgery

Under local analgesia, a linear skin incision and an underlying burr hole were made. The dura was opened, and the hematoma was evacuated via irrigation with warm Ringer's saline. After evacuation, a subperiosteal [13] or subdural drain [14] was placed based on the surgeon's preference. The drain was connected to a continuous closed-system and maintained in place for at least 12 h or until production stopped. The following morning, the assigned drug treatment (i.e., placebo or active compound) was initiated and continued daily for 90 days. Any platelet anti-aggregant therapy was discontinued seven days preoperatively when possible. In acute cases, platelet suspensions were given perioperatively. For patients on anticoagulation therapy with International Normalized Ratios (INRs) exceeding 1.5 at the time of surgery, the effects of the anticoagulation medication were reversed prior to surgery. Anti-aggregant or anticoagulation therapy was re-initiated four to six weeks postoperatively or earlier if indicated.

Measurements of blood potassium, sodium, creatinine and urea and blood pressure were performed at one day, one week and two weeks following the initiation of the assigned drug treatment.

A scheduled CTC was performed after six weeks or earlier in cases with symptoms of recurrence. If a significant CSH remnant was present at the six-week control CTC, and the patient was asymptomatic, an additional CTC was performed three months postoperatively. In cases in which the patient developed a recurrence of the symptoms of CSH (i.e., headache, nausea, vomiting and neurological deficits) and exhibited a significant remnant on CTC, re-evacuations were performed.

Recurrence was defined as an ipsilateral CSH requiring surgical evacuation within a three-month period.

Follow-ups were performed three months after surgery. At the follow-up, CSH recurrence, GCS, blood pressure, neurological deficits, headache and nausea/vomiting were noted. The size of the remnant CSH at the six-week control CTC was measured.

2.3. Non-randomized patient group

The patient charts and CTCs of the patients who were not randomized in the study were examined and the following information was noted: (1) the reason for lack of inclusion in the randomized portion of the study, (2) the size of the CSH, (3) age, (4) gender, (5) recurrence and (6) ACE inhibitor treatment.

2.4. Data analyses

The data were analyzed as intention to treat.

The size of the CSH was measured on CTC or MRC preoperatively and at the six-week control scan. The measurements were performed by blinded observers using the XYZ/2 method described by Sucu et al. (2005) [19]. The data were analyzed using Excel (Microsoft 2007) and GraphPad Prism 6. Statistical analyses were

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