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Clinical Study

Preoperative angiotensin converting enzyme inhibitor usage in patients with chronic subdural hematoma: Associations with initial presentation and clinical outcome

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ABSTRACT

The aim of this study is to analyze the association of preoperative usage of angiotensin converting enzyme (ACE) inhibitors with the initial presentation and clinical outcome of patients with chronic subdural hematoma (cSDH). Patients treated for cSDH between 2009 and 2013 at our institution were included in this retrospective case-control study. Medical charts were reviewed retrospectively and data were analyzed using descriptive and inferential statistics. Out of 203 patients (58 females, mean age 73.2 years), 53 (26%) patients were on ACE inhibitors before their presentation with cSDH. Median initial hematoma volume in individuals with ACE inhibitors (179.2 ± standard error of the mean [SEM] 13.0 ml) was significantly higher compared to patients without ACE inhibitors (140.4 ± SEM 6.2 ml; $p = 0.007$). There was an increased probability of surgical reintervention in the ACE inhibitor group (12/53, 23% *versus* 19/153, 12%; $p = 0.079$), especially in patients older than 80 years (6/23, 26% *versus* 3/45, 7%; $p = 0.026$). ACE inhibitors are associated with higher hematoma volume in patients with cSDH and with a higher frequency of recurrences requiring surgery (especially in the very old). We hypothesize that these effects are due to ACE inhibitor induced bradykinin elevation causing increased vascular permeability of the highly vascularized neomembranes in cSDH.

1. Introduction

Chronic subdural hematoma (cSDH) is one of the most common entities treated by neurosurgeons. As cSDH has a high prevalence in the very old it will become an increasingly important public health issue in the context of global aging [1]. It is agreed that the organization of a hematoma and the formation of highly-vascularized neomembranes with fragile capillaries and subsequent micro-hemorrhage is the mainstay of cSDH pathophysiology [2–5]. Several studies have also linked cSDH enlargement to hyperfibrinolytic activity during liquefaction of the hematoma [6–10]. The plasma enzyme plasmin is not only the chief agent of hyperfibrinolysis, but also an activator of the kallikrein-kinin system. The end product of the kallikrein-kinin system is bradykinin, a powerful vasoactive peptide that induces both increased vascular permeability and vasodilation [11,12]. Fujisawa et al. showed that the activation of the kallikrein-kinin system in cSDH patients causes increasing vascular permeability with subsequent hematoma enlargement due to blood extravasation from neomembranes [13].

The rationale to investigate angiotensin converting enzyme (ACE) inhibitors in the setting of cSDH is that ACE inhibitors are known to cause elevated levels of bradykinin [14,15], the end-product of the kallikrein-kinin system that has been linked to enlargement of cSDH hematoma volume. The existing literature on the association between ACE inhibitors and cSDH is scarce and results have been mixed [16,17].

2. Patients and methods

2.1. Patients

Medical charts and radiological images of hematoma patients operated at our institution between the 2006 and 2013 were reviewed retrospectively. Patients were only included in this study if sufficient information on symptomatology, comorbidities, medications and postoperative imaging in three-plane reconstructions

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were available. Also, patients needed to have at least one well-documented outpatient follow-up visit. This retrospective case-control study was conducted in accordance with federal legal requirements and a waiver was obtained from the Local Ethics Committee (KEK-StV-Nr. 33/14).

2.2. Surgical management

Surgery was performed in patients with symptomatic and/or large hematomas (>10 mm thickness). In patients with large bilateral hematomas, surgery was performed on both sides. All patients with a clear indication for surgery were operated upon within 24 hours, except for patients with non-emergent symptoms on oral anticoagulation or antiplatelet medications. The latter subjects were watched closely until blood clotting and thrombus functions were restored (watch and wait in patients on antiplatelet medications and vitamin K supplementation in patients on coumarins). Patients were operated under general anesthesia and using subperiosteal drains as described previously [18,19]. In brief, patients were placed in a supine position using a plastic ring (unilateral cSDH) or a horseshoe headrest (bilateral cSDH). Usually, double burr-hole trepanations were placed on each side, in most cases the frontal burr-hole was placed at the junction of the superior temporal line and the coronal suture (stephanion), while the posterior burr-hole was placed in the region of the parietal eminence. Postoperatively, the patients were put on a bed-restriction with the head of the bed flat (0°) and mild overhydration until the subperiosteal drains were removed after 48 hours. ACE inhibitors and angiotensin receptor blocker that patients were treated with prior to admission were continued peri- and postoperatively.

2.3. Imaging analysis

CT images were analyzed using the last available image before the intervention and all follow-up images. We used the formula XYZ/2 (maximum width × maximum depth × maximum length; not necessarily on the same slide) to calculate cSDH volume as described by Sucu et al. [20] The XYZ/2 method showed excellent correlation (rho 0.932; $p < 0.001$) with computer-assisted volumetric analyses in patients with cSDH [20]. In patients with bilateral cSDH, the hematoma volume of both sides was added.

2.4. Statistical testing

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20 (IBM, Armonk, NY, USA) and figures were generated using GraphPad Prism (GraphPad Software, San Diego, CA, USA). Continuous variables are presented as mean ± standard error of the mean. Comparisons between groups were done using the Mann–Whitney–U test for continuous parameters and for categorical parameters we used the Chi-square test or the Fisher's exact test, where appropriate. To corroborate the results of bivariate testing, we constructed a generalized linear model with initial hematoma volume as the dependent variable. Within-subjects factors were ACE-inhibitor group and sex, and age was a covariate. Statistical significance was established at the alpha level of $p = 0.05$.

3. Results

A total of 203 patients who met the above inclusion criteria were included in this study. A group of 53 patients was treated with ACE inhibitors at the time of admission to our department and a control group of 150 patients had not previously received ACE inhibitor treatment. There was a clear male predominance in our study population with a male-to-female ratio of almost 3:1 (146 males and 57 females). This male predominance was even more prominent in the ACE inhibitor group (43 males and 10 females; ratio 4:1) compared to the patients without ACE inhibitors (103 males and 47 females; ratio 2:1). Patients in the ACE inhibitor group were older (77.8 ± 1.4 years) and had a higher body mass index (BMI; 26.6 ± 0.7 kg/m^2) compared to controls (72.32 ± 1.1 years and 24.7 ± 0.4 kg/m^2). The reported rate of previous head trauma and the rate of bilateral cSDH were similar in both groups with half of the patients reporting previous trauma and one-third of the patients presenting with bilateral cSDH. Basic patient characteristics are summarized in Table 1.

3.1. Symptoms at presentation and comorbidities

In the overall patient population (n = 203) gait instability was the most frequent symptom (53%) followed by motor deficits (41%) and headache (40%). Other symptoms such as dysphasia (27%), disorientation (25%) and memory deficits (23%) were less frequent. Initial symptoms are summarized in Table 2. The distribution of symptoms was similar in both groups (ACE inhibitors *versus* controls), except for dysphasia which was more pronounced in the ACE inhibitor group (38% *versus* 23%) and headache which was more frequent in controls (45% *versus* 26%).

Regarding comorbidities at presentation, arterial hypertension and a history of cardiovascular disease were by far the most frequent (51% and 47% in the overall patient population, respectively). As expected, arterial hypertension, cardiovascular disease and renal disease were overrepresented in the ACE inhibitor group

Table 1
Basic chronic subdural hematoma patient characteristics

	All (n = 203)	ACE inhibitors (n = 53)	No ACE inhibitors (n = 150)
Sex (Males/Females)	146/57	43/10	103/47
Age, years	73.8 ± 0.9	77.8 ± 1.4	72.3 ± 1.1
BMI, kg/m^2	25.2 ± 0.4	26.6 ± 0.7	24.7 ± 0.4
Previous head trauma	102 (50%)	25 (47%)	77 (51%)
Bilateral cSDH	68 (34%)	18 (34%)	50 (33%)

Data are presented as mean ± standard error of the mean or number (%) unless otherwise indicated.
ACE = angiotensin converting enzyme, BMI = body mass index, cSDH = chronic subdural hematoma.

Table 2
Symptoms and comorbidities in patients with chronic subdural hematoma

Symptoms at presentation	All (n = 203)	ACE inhibitors (n = 53)	No ACE inhibitors (n = 150)
Motor deficit	84 (41%)	26 (49%)	58 (39%)
Headache	81 (40%)	14 (26%)	67 (45%)
Disorientation	51 (25%)	16 (30%)	35 (23%)
Dysphasia	55 (27%)	20 (38%)	35 (23%)
Anisocoria	11 (5%)	2 (4%)	9 (6%)
Seizure	15 (7%)	4 (8%)	11 (7%)
Memory deficits	47 (23%)	13 (25%)	34 (23%)
Gait instability	108 (53%)	31 (59%)	77 (51%)
Comorbidities			
Diabetes	23 (11%)	6 (11%)	17 (11%)
Arterial hypertension	104 (51%)	41 (77%)	63 (42%)
Cardiovascular	96 (47%)	38 (72%)	58 (39%)
Previous stroke	19 (9%)	9 (17%)	10 (7%)
Renal disease	27 (13%)	13 (25%)	14 (9%)
Liver cirrhosis	11 (5%)	3 (6%)	8 (5%)
Alcohol abuse	19 (9%)	6 (11%)	13 (9%)

ACE = angiotensin converting enzyme.