Effect of angiotensin converting enzyme inhibitors on the development of chronic subdural haematoma

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Aims. Angiotensin converting enzyme inhibitors (ACEI) have been recently discussed in connection with the medical treatment of chronic subdural haematoma (CSDH). They may improve the treatment results. The objective of our study was to evaluate the impact of ACEI on the development of CSDH. The first question was to assess the impact of ACEI on postoperative CSDH healing. The second was to assess the impact of ACEI on the development of CSDH as such.
Patients and Methods. The study recruited patients treated surgically for CSDH at our department in the 2013–2018 period. Based on medical records, we retrospectively evaluated the clinical condition of the patients, their history (mainly pharmacological – the use of ACEI) and the course of treatment focussing on the reoccurrence of disease necessitating further therapeutic interventions. For the purpose of evaluating the impact of ACEI on postoperative CSDH healing, the patients were divided into two groups: those using ACEI and those without this medication. The results were compared. We also compared the prevalence of ACEI use in patients with CSDH with the prevalence of ACEI in the comparable population. The difference of the rates allowed us to evaluate the impact of ACEI on the development of CSDH itself.
Results. Of the 217 patients after surgery for CSDH, 79 continued the use of ACEI; the remaining 138 patients did not use this medication. Patients using ACEI after the surgery experienced a recurrence in 24 (30.4%) cases; patients without ACEI in 37 (26.8%) cases. A negligibly higher number of recurrences was recorded in patients with postoperative use of ACEI, but this difference was not statistically significant (P=0.574). Of a total of 230 patients who underwent surgery for CSDH, 81 were using ACEI chronically (35.2%). In the control group of 100 patients, 38 (38.0%) patients used ACEI. The difference was not statistically significant (P=0.629), so it is not possible to assume that ACEIs influence the development of CSDH as such.
Conclusion. The initial high hopes for a positive ACEI effect on the healing of CSDH are now waived after the publication of several recent studies. According to our present knowledge, the development of CSDH does not appear to be influenced by ACEI use.

Key words: chronic subdural haematoma, angiotensin converting enzyme inhibitors, recurrence, burr hole drainage

Received: March 24, 2020; Revised: June 24, 2020; Accepted: June 25, 2020; Available online: July 16, 2020
https://doi.org/10.5507/bp.2020.029

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INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) have been recently discussed in connection with the medical treatment of chronic subdural haematoma (CSDH). They may improve the treatment results. The most frequently used representatives of the class include perindopril, captopril, ramipril, lisinopril, fosinopril, quinapril and trandolapril. The above drugs are primarily used to treat arterial hypertension, chronic cardiac failure and acute myocardial infarction, and they are also used as renoprotective drugs. ACEI were also shown to positively influence endothelial function. According to a study by Weigl et al., ACEI are drugs holding great promise in the treatment of CSDH as well; the study demonstrateds a marked reduction of postoperative recurrences, and even reduced probability of the development of CSDH in patients using ACEI (ref.[1]). In contrast, other studies do not show any effect of ACEI on the course of healing CSDH (ref.[2,3]). Neidert et al. even showed a higher recurrence rate in patients using ACEI (ref.[4]). The effect of ACEI on the healing of CSDH is still unclear. The objective of our study was to evaluate the impact of ACEI on the development of CSDH. The first question was to assess the impact of ACEI on postoperative CSDH healing. The second was to assess the impact of ACEI on the development of CSDH as such.

PATIENTS AND METHODS

The study recruited patients treated surgically for CSDH at our neurosurgical department in the 2013–2018 period. The indication for surgical treatment was symptomatic CSDH with a CT image of CSDH behaving expansively. The study excluded patients with hydromas or

hygromas. The surgical procedure consisted of one burr hole and subdural drainage. Operations were performed under local anaesthesia. Follow-up brain CT scans with outpatient examination in uncomplicated cases were performed 6 weeks after surgery, then after 6 months. In the case of a complicated postoperative course, follow-up with CT scans was individualised and repeated.

Medical records were evaluated retrospectively in terms of patient clinical condition (prior to surgery, at discharge, and at subsequent follow-ups), medical history (mainly pharmacological – use of ACEI) and the course of treatment with a focus on disease recurrence. We defined recurrence as a state in which there was a repeated deterioration of the clinical condition or persisting clinical complaints in the postoperative period with corresponding CT findings of a subdural collection with expansive behaviour. In such cases, another therapeutic intervention was carried out (puncture and evacuation of the subdural collection via the original burr hole, new burr hole drainage, or craniotomy and membranectomy).

For the purpose of evaluating the impact of ACEI on postoperative CSDH healing, the patients were divided into two groups: those using ACEI and those without this medication. The results were compared. We also compared the extent of ACEI use in patients with CSDH with the extent of ACEI in a comparable population. The difference in the rates allowed us to evaluate the impact of ACEI on the development of CSDH itself. One hundred patients, of similar as the patients with CSDH, were randomly selected for the control group from patients who also underwent surgery at our department in the 2013-2018 period for a diagnosis other than CSDH (degenerative spine disease, cerebral tumour, carpal or cubital tunnel syndrome, vertebral fracture).

The data were processed statistically using the chi-square test or Fishers exact test, using the statistical software IBM SPSS Statistics, version 22, with the significance level of 0.05.

RESULTS

Of the 217 patients included in the study, 79 continued the use of ACEI after surgery for CSDH; the remaining 138 did not use this medication. The basic demographical data were not statistically significantly different between groups (Table 1). Of patients using ACEI after surgery, 24 (30.4%) patients experienced recurrence, 6 (7.6%) of whom had to undergo craniotomy and membranectomy after the failure of less invasive procedures. 37 (26.8%) patients without ACEI developed recurrence post-surgery, of whom 7 (5.1%) patients had to undergo membranectomy. A negligibly higher number of recurrences were recorded in patients with postoperative use of ACEI, however, this difference was not statistically significant (P=0.574) (Table 2). Of the 230 patients who underwent surgery for CSDH, 81 (35.2%) were using ACEI chronically. In the control group of 100 patients, 38 (38.0%) patients used ACEI. The difference is not statistically significant (P=0.629). For this reason, it cannot be concluded that the ACEI influenced the development of CSDH as such. The groups did not significantly differ on the basis of this demographic data (Table 3). The perioperative mortality rate in our cohort was 5.7% (13 patients died periopera-

Table 1. Characteristics of patients undergoing surgery for CSDH in consideration of postoperative use of ACEI.

	Without ACEI (n = 138)	With ACEI (n = 79)	Overall (n = 217)	*P*
Age (years), median (min-max)	74.0 (30-92)	73.0 (28-90)	74.0 (28 - 92)	0.789
Gender: males	89 (64.5%)	50 (63.3%)	139 (64.1%)	0.859
females	49 (35.5%)	29 (36.7%)	78 (35.9%)	
Body side: right	62 (44.9%)	37 (46.8%)	99 (45.6%)	
left	65 (47%)	35 (44.3%)	100 (46.1%)	0.917
bilateral	11 (8.0%)	7 (8.9%)	18 (8.3%)	
Antiplatelet therapy	27 (19.6%)	15 (19.0%)	42 (19.3%)	0.917
Anticoagulant use	15 (10.9%)	10 (12.7%)	25 (11.5%)	0.691

Table 2. Evaluation of the effect of ACEI on postoperative CSDH healing.

	Without ACEI (n = 138)	With ACEI (n = 79)	Overall (n = 217)	*P*
Burr hole drainage with curative effect	101 (73.2 %)	55 (69.6 %)	156 (71.9 %)	0.574
Recurrence necessitating further intervention	37 (26.8%)	24 (30.4%)	61 (28.1%)	0.574
puncture	22 (15.9%)	15 (19.0%)	37 (17.1%)	0.566
new burr hole	8 (5.8%)	3 (3.8%)	11 (5.1%)	0.750
membranectomy	7 (5.1%)	6 (7.6%)	13 (6.0%)	0.554

Table 3. Comparison of patients treated for CSDH with the control group in consideration of the rate of use of ACEI.

	Surgery for CSDH (n = 230)	Control group (n = 100)	Overall (n = 330)	*P*
Age (years), median (min-max)	74.0 (28-95)	72.0 (37-86)	73.5 (28-95)	0.712
Gender: males (%)	147 (63.9%)	58 (58.0%)	205 (62.1%)	0.309
females (%)	83 (36.1%)	42 (42.0%)	125 (37.9%)	
ACEI use	81 (35.2%)	38 (38.0%)	119 (36.1%)	0.629

tively out of 230 patients operated on for CSDH). These patients were not in the first patient cohort, where we evaluated the effect of ACEI on postoperative CSDH healing.

DISCUSSION

ACEI are drugs that block the angiotensin converting enzyme and prevent the transformation of angiotensin I to angiotensin II, which is one of the many steps in the complex renin-angiotensin-aldosterone system. This system primarily participates in the control of blood pressure, mineral and water balance, and tension of the vascular wall. ACEI are mainly used in the treatment of arterial hypertension and cardiac failure. The drugs were also shown to have a beneficial renoprotective effect, particularly in diabetic nephropathy. They are capable of positive tissue remodelling, not only of cardiac ventricles, but also the vessels themselves. They positively impact the function of damaged vascular endothelium. Weigel et al. also assume an antiangiogenic effect of ACEI. Patients treated with ACEI have been shown to have lower levels of the vascular endothelial growth factor, a substance stimulating angiogenesis, in the liquid portion of haematoma obtained during CSDH surgery[1].

A significant pathophysiological mechanism leading to size progression of CSDH is the formation of neocapillaries in the external capsule of the haematoma. These capillaries are thin, without contiguous endothelial lining, fragile and with increased permeability, which results in repeated bleeding and increased secretion in the haematoma cavity[5-7]. A possible positive influence of ACEI on the healing of CSDH could thus be explained as improved endothelial function in the neocapillaries, especially their reduced formation. Weigel et al. confirm their pathophysiological explanation with clinical results: they demonstrated in a cohort of 310 patients that the number of postoperative CSDH recurrences was significantly lower in patients using ACEI than in patients without ACEI (5% vs. 18%). Moreover, only 25% of patients treated for CSDH used ACEI, while this was 40% in the control group. Based on this they concluded that ACEI act against the development of CSDH[1]. The conclusion of the retrospective study by Neidert at al. presenting completely opposing results is of interest. They diagnosed much larger haematoma volumes in patients using ACEI compared to patients without ACEI, and also recorded a higher number of recurrences in patients using ACEI (23% vs. 12%). The authors assume that this fact could be explained by the increased level of bradykinin due to the use of ACEI, which act to increase the permeability of neocapillaries in the haematoma capsule[4]. A prospective randomised study by Poulsen at al. tested the effect of perindopril versus placebo on postoperative CSDH healing, and found no difference between the procedures[2]. An extensive Scandinavian multicentric retrospective study came to a similar conclusion[3].

Our cohort of patients treated surgically for CSDH also failed to demonstrate any significant difference in the number of recurrences between patients using ACEI and patients without this medication. The initially held hopes of a positive ACEI effect during CSDH healing now appear uncertain.

CONCLUSION

The initially high hopes for a positive ACEI effect on the healing of CSDH are now waived after the publication of several recent studies. According to our present knowledge, the development of CSDH does not appear to be influenced by ACEI use.

ABBREVIATIONS

ACEI, Angiotensin converting enzyme inhibitors; CSDH, Chronic subdural haematoma; CT, Computed tomography.

Acknowledgements: No funding was received for this research.
Author contributions: All authors contributed equally to preparing the manuscript.
Conflict of interest statement: None declared.

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