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Odense December 10th 2013

To Prof. P.M. Klinge
Editor
Clinical Neurology and Neurosurgery

From Frantz Rom Poulsen, MD, PhD
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Re: Submission of the manuscript ”**No effect of Angiotensin Converting Enzyme inhibitors on volume of residual chronic subdural haematoma six weeks after burr hole surgery, a randomized trial**”

Dear editor,

We hereby submit the manuscript ”No effect of Angiotensin Converting Enzyme inhibitors on volume of residual chronic subdural haematoma six weeks after burr hole surgery” for consideration for publication in *Clinical Neurology and Neurosurgery*.

As described in the manuscript previous studies have suggested that treatment with angiotensin converting enzyme inhibitors can reduce the recurrence risk after surgical treatment.

This study was designed to test this hypothesis and includes a prospective double blinded randomized part and a retrospective part.

We found no effect of ACE inhibitor treatment on residual chronic subdural hematoma measured on control CT scans six weeks after surgery in the randomized part of the study. Similarly, the retrospective analysis of the patients not randomized revealed no effect of ACE inhibitor treatment on chronic subdural hematoma recurrence.

To our knowledge this is the first double blinded randomized controlled clinical trial to investigate if ACE inhibitors can reduce the risk of chronic subdural hematoma recurrence after surgical evacuation.

Part of this paper was presented as a poster at Congress of Neurological Surgeons 2013 Annual Meeting, October 2013.

All authors have approved the manuscript prior to submission. The authors have no conflict of interests or financial disclosures to report. The study was approved by the Danish Health Research Ethics Committee, Danish Health and Medicines Authority and the Danish Data Protection Agency, and conducted in accordance with Good Clinical Practice.

On behalf of the authors, sincerely

Frantz Rom Poulsen.

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No effect of Angiotensin Converting Enzyme inhibitors on volume of residual chronic subdural hematoma six weeks after burr hole surgery, a randomized trial

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None of the authors have any personal or institutional financial interest in the drug described in the present submission.

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Abbreviations

CSH, chronic subdural hematoma; ACE, angiotensin converting enzyme; CTC, cerebral computed tomography scan; MAP, mean arterial blood pressure; GCS, Glasgow coma scale

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ABSTRACT

OBJECTIVE: Recurrence rates between 5 and 25% have been reported after surgery for Chronic Subdural Hematoma (CSH). Previously, a study has shown that treatment with Angiotensin Converting Enzyme (ACE) inhibitors decrease the recurrence risk. To test the effect of ACE inhibitors on CSH recurrence or remnant we conducted a prospective double blinded randomized controlled clinical trial on patients with CSH from July 2009 till October 2012.

PATIENTS AND METHODS: Patients eligible to burr hole surgery for CSH were prior to surgery randomized to either the ACE inhibitor perindopril 5 mg or placebo treatment daily for three months. Cerebral CT scan was performed after six weeks. Follow up three months after surgery. In addition, a retrospective analysis of data and CT scans from all not randomized patients from the same time period was performed.

RESULTS: 47 patients were included in the randomized study. Preoperative Glasgow Coma Scale was 15. No patients in the randomized group developed recurrence after surgery. Measurement of the size of CSH pre- and six weeks post operatively revealed no difference in the size of residual CSH between placebo and perindopril treated groups.

In the retrospective group (245 patients) there was no correlation between risk of recurrence and ACE inhibitor treatment.

CONCLUSION: Perindopril does not diminish residual CSH six weeks after burr hole surgery and based on our retrospective analysis ACE inhibitors do not decrease the risk of CSH recurrence.

Running Title No effect of ACE inhibitors on residual chronic subdural hematoma size and recurrence

Keywords Hematoma, Subdural, Chronic, Angiotensin-Converting Enzyme Inhibitors, Recurrence

INTRODUCTION

A common acute and sub-acute neurosurgical condition is chronic subdural haematoma (CSH) [1-4].

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

Other studies have focused on the outer membrane and its immature and leaky blood vessels. Analysis of haematoma fluid and the outer membrane has revealed several angiogenesis promoting factors including Vascular Endothelial Growth Factor (VEGF) and its signalling pathway. Although the cellular origin of these growth factors have not been established [5-12] the presence of VEGF in haematoma fluid has been hypothesized to induce angiogenesis of the immature and leaky blood vessels thereby promoting growth and recurrence of CSH.

The treatment of symptom giving CSH is surgical. Most often a burr hole with opening of the dura and underlying neomembrane is performed followed by thorough rinsing and closed subperiostal [13] or subdural drainage [14]. In case of a newer CSH with appearance of several membranes on cerebral computed tomography scan (CTC), a craniotomy may be necessary.

Regardless of surgical method the risk of recurrence is reported as high as 25% [3, 15].

Angiotensin Converting Enzyme (ACE) inhibitors are well-established compounds in the treatment of arterial hypertension. ACE inhibitors have also been shown to inhibit development of new blood vessels in the retina of diabetic patients [16-18]. In addition, a combined prospective and retrospective study have shown that patients treated with ACE inhibitors regardless of dose and generic compound have less risk of developing CSH, and in those patients who developed CSH the risk of recurrence was reduced from 18 to 5%. The mechanism is unknown, but it has been proposed that ACE inhibitors can reduce the development of new and immature blood vessels in the neomembrane via a diminished production of VEGF [6], thereby reducing the extravasation of fluid into the CSH.

The present prospective and double-blinded randomized controlled study was designed to investigate if treatment with the widely used ACE inhibitor perindopril could reduce the amount of residual CSH

fluid present on six weeks control CTC after burr hole treatment for CSH and subsequently the risk of recurrence.

METHODS

The study was approved by the Danish Health Research Ethics Committee, Danish Health and Medicines Authority and the Danish Data Protection Agency, and conducted in accordance with Good Clinical Practice. It included all patients submitted to a medium sized neurosurgical department in Denmark (single center) from July 2009 till October 2012 (follow-up of last randomized patient).

Data was evaluated after inclusion of 47 patients (randomization ID 50 out of the 100 patients intended for inclusion).

Randomization and masking

Patients with CTC or cerebral magnetic resonance imaging (MRC) verified CSH and symptoms requiring surgery were eligible for inclusion. Inclusion criteria were patients with CSH, indication for burr hole surgery, and minimum 18 years of age. Exclusion criteria were lack of compliance including impaired consciousness, renal artery or aorta stenosis, impaired renal function, allergy or intolerance toward ACE inhibitors, coagulopathy, malignant disease, fertile women, severe neurological disorders and treatment with drugs contra indicating treatment with ACE inhibitors. Diabetic patients had their blood glucose levels measured four times daily the first 3 days after randomization. Upon admittance informed consent was obtained and the patients were double blindly randomized to 90 days oral treatment with either placebo or perindopril 5 mg (Coversyl®) ingested daily in the morning. Randomization was performed in advance and randomized patients were assigned a randomization ID corresponding to appropriate treatment. Both placebo and perindopril tablets were individually wrapped in small lactose containers easy to swallow making it impossible to distinguish placebo from active compound. Background information including age, gender, history of head trauma, anti coagulation treatment, blood pressure, heart rate, Glasgow Coma Scale (GCS), neurological deficits, headache, nausea/vomiting and size of CSH were recorded. Included patients received a diary, in which the patient made a mark each day the medicine was ingested. Possible side effects were noted.

Blood sample analysis including measurements of blood potassium, sodium, creatinine and urea was 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 data after inclusion of half of the intended patient population was performed.

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 European Medicines Agency (EMEA), EudraCT number 2009-010058-37.

Surgery

In local analgesia, a linear skin incision and an underlying burr hole was made. Dura was opened and the hematoma evacuated using irrigation with warm Ringer saline. After evacuation a subperiostal [13] or subdural drain [14] was placed as to the surgeons preference. The drain was connected to a continuous closed-system and kept in place for at least 12 hours or till production stopped. The morning after surgery, the assigned drug treatment (placebo/active compound) was initiated and continued daily for 90 days. Any platelet anti-aggregant therapy was discontinued 7 days preoperatively if possible. In acute cases portions of platelet suspensions were given per operatively. If patients in anticoagulation therapy had an International Normalized Ratio (INR) exceeding 1.5 at the time of surgery, the effects of the anticoagulation medication was reversed before surgery. Anti-aggregant or anticoagulation therapy was re-initiated four to six weeks postoperatively.

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

A control CTC was performed after six weeks, earlier in case of symptoms of recurrence. If significant CSH remnant was present at the six weeks control CTC and the patient where asymptomatic an additional CTC was performed three months postoperatively. Renewed surgical evacuation after control CTC, was performed at the surgeons preference.

Recurrence was defined as ipsilateral CSH needing surgical evacuation within the three months period.

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

Non-randomized not included group

The patient charts and CTC of patients not included in the study were examined and 1) reason for lack of inclusion, 2) size of CSH, 3) age, 4) gender and 5) ACE inhibitor treatment was registered. In addition, recurrence frequency in this group was determined.

Data analysis

Data were analyzed as intention to treat.

The size of CSH was measured on CTC or MRC preoperatively and at the six weeks control scan. Measurements were performed using the XYZ/2 method as described by Sucu et al (2005) [19]. Data were analyzed using Excel (Microsoft 2007) and Graphpad Prism 6. Statistical analysis was performed using Student t-test, Fischers exact test or Chi^2 test. Statistical significance was defined as $P < 0.05$.

RESULTS

In total 295 patients with CSH were submitted to the neurosurgical department for surgical evacuation during the study period.

The study was discontinued after inclusion of slightly less than half of the intended patient number (48 patients randomized, last patient randomization ID 50) since planned interim analysis of the data showed no difference between the placebo treated and perindopril treated group, and none of the included patients developed recurrence.

Randomized group

Fifty patients fulfilled the inclusion criteria and were included and randomized. Three patients withdraw their consent prior to treatment and were excluded from the study. Included were therefore

placebo (22, 17 male and 5 female) or perindopril 5 mg (25, 21 male and 4 female) treated patients. Demographic data on included patients are summarized in Table 1. The mean age was 70.5 years in the placebo group and 64.3 years in the perindopril group (total mean 67.2 years). Thirty-two patients had a history of known head trauma one to 20 weeks prior to hospitalization (mean 7 weeks). Eleven out of 48 used per oral anticoagulation or platelet anti-aggregant treatment. The preoperative GCS of included randomized patients was 15. The CSH was located over the right hemisphere in 22 patients, over the left hemisphere in 16 patients and where bilateral in nine patients. In the bilateral CSH group both sides were evacuated in five cases and the right side alone was evacuated in four cases.

Mean arterial blood pressure (MAP) was measured preoperatively. No statistical significance was found comparing the two treatment groups (placebo: 103 mmHg, perindopril: 104 mmHg, P = 0.88).

There was no statistical significant difference in the size of CSH preoperatively in the two treatment groups (placebo: 130 cm^3, perindopril: 124 cm^3, mean 127 cm^3, P = 0.72, Fig. 1).

No patients experienced recurrence in the randomized group.

Measurements of the CSH remnant size six weeks postoperatively revealed a mean remnant size in the placebo group of 28.4 cm^3 and 22.8 cm^3 in the perindopril group (P = 0.50, Fig. 1).

Two patients in the perindopril treated group experienced a dry cough during the treatment period. This cough disappeared upon discontinuation of the compound after 3 months treatment. No serious side effects were noted. Additional two patients in the perindopril treated group discontinued the treatment after days to weeks.

Not randomized not included group

248 patients (173 males and 75 females) were not included in the study. Their patient charts were reviewed retrospectively. The reasons for their exclusion are listed in Table 2. For patient demographic data, see Table 3. The mean age in this group was 75.5 years (P < 0.05 compared to the mean age in the randomized group). The average size of CSH preoperatively was 112 cm^3 compared to 127 cm^3 in the randomized group (P = 0.08). Thirty-five cases were bilateral CSH. In 40 patients CTC were not available for analysis. Data from three patients were not available. 90 out of the 245 not randomized and not included patients were in ACE inhibitor treatment prior to surgery. The

recurrence rate in this ACE inhibitor treated group were 16.7% whereas the corresponding recurrence rate in the group of not randomized patients receiving no ACE inhibitor treatment was 18.1% (NS., Fig. 2)

Among the 245 patients 43 were treated at least once for recurrence leading to a total recurrence rate of 17.6% (43 recurrences out of 245 patients) thus yielding a total risk of recurrence (randomized and not randomized not included group in total) of 14.7%.

DISCUSSION

Previous studies have suggested that treatment with ACE inhibitors can reduce the recurrence rate after surgical evacuation of CSH [6]. The present study was designed to test this hypothesis in a randomized controlled clinical trial setting.

None of the patients in the randomized group experienced recurrence irrespective of three months treatment with placebo or ACE inhibitor. The reason for this is not known. In addition, there was no statistically significant difference in the size of CSH in the randomized group compared with the not randomized not included group, although absolute values indicate that the pre operative size of CSH were slightly larger in the randomized group. There was no difference in the methods of surgical intervention. The study was discontinued after planned interim analysis. Therefore only half of the intended 100 patients were randomized. The intention of including 100 patients in this study was based on a power calculation on the basis of data from Weigel et al[6], where 18% of patients not in ACE inhibitor treatment developed recurrence, whereas this was the case for only 5% of patients in ACE inhibitor treatment. In the present study this should correspond to 4 patients in the placebo treated group and > 1 patient in the perindopril treated group.

The randomized group does however, represent a selected subgroup of patients with CSH. Since the patients should be able to understand and accept participation in the study, no dementia or otherwise cognitive impaired patients or patients with impaired level of consciousness were included and randomized (all randomized patients had GCS 14-15). In addition, the average age in the randomized group were 8.3 years less than in the not randomized group.

The overall recurrence rate of 14.7% (included and not-included patients) is comparable to recurrence rates described in the literature. The surgical routine in this study was using either a subperiostal or a subdural closed drainage system for at least 12 hours postoperatively. A subdural or subperiostal drain after evacuation and rinsing has been associated with a lower recurrence risk than no drain [13, 14, 20].

In the retrospective part of this study the use of ACE inhibitors of not randomized and not included patients was investigated and correlated to CSH recurrence rate. There was no statistical significant difference in recurrence rates between patients with or without ACE inhibitor treatment.

Several factors have been shown to increase the risk of recurrence of CSH after surgical evacuation. Recently, this has been studied in a prospective study based on CT scans where predictors for postoperative recurrence were 1) preoperative hematoma volume, 2) imaging characteristics of the hematoma and 3) residual total hematoma cavity volume on the 1st postoperative day [21], i.e. the ability of the brain to expand itself after surgical evacuation of the hematoma compressing it. This study found a recurrence risk of 15.9%. In the present study all recurrences were found in the not randomized group.

A male predominance was observed in both the randomized and not randomized group. This is in accordance with previous studies showing that CSH is more common in males than in females [22].

The main reasons for exclusion from the randomized group were confusion or low GCS, pre-existing ACE inhibitor treatment or unknown. The designation ”unknown” includes patients that could be included but due to busy clinical work was not. However, since the size of remnant CSH at the six weeks control CTC in the randomized group revealed no difference between placebo and perindopril we conclude that daily 3 months postoperative administration of ACE inhibitor has no effect in the treatment of CSH after surgical evacuation in awake compliant patients with GCS 14-15. This is further supported by the retrospective part of this study.

FIGURE CAPTIONS

Figure 1 Bar graph illustrating the mean size of CSH preoperatively and at six weeks control CTC in the placebo and perindopril treated groups. No statistically significant difference (NS., t-test) between the two groups was found.

CSH: chronic subdural hematoma; SEM: standard error of mean

Figure 2 Bar graph illustrating the number of patients in the not included and not randomized group experiencing recurrence. No statistically significant difference in recurrence rate was observed comparing patients in pre-existing ACE inhibitor treatment with patients receiving no ACE inhibitor (NS., Fishers exact test).

CSH: chronic subdural hematoma; ACE: angiotensin converting enzyme

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Table(s)

Table 1. Demographic data on patients with chronic subdural hematomas (CSH) randomized in the present study

	Placebo	**Perindopril 5 mg**	**P-value**
Number of patients	22	25	-
Age (years)	70.5	64.3	0.11 (t-test)
Sex	17 M, 5 F	21 M, 4 F	0.31 (Chi^2 test)
Preoperative GCS	15	15	0.33 (t-test)
Mean arterial blood pressure preoperatively (MAP, mmHg)	103	104	0.88 (t-test)
Mean arterial blood pressure at three months follow-up (MAP, mmHg)	103	102	0.80 (t-test)
Mean size of CSH preoperatively (cm^3)	130	124	0.88
Mean size of CSH at six weeks control CTC (cm^3)	28.4	22.8	0.50
Recurrence	0	0	-

GCS: Glasgow coma scale; MAP; mean arterial blood pressure; CSH: chronic subdural hematoma

Table(s)

Table 2. Reasons for exclusion in the randomized group	Number of patients
Confusion/low GCS	55
Known coagulopathy	1
Known cancer	5
Already in ACE inhibitor treatment	44
No patient consent obtained	11
Contraindications for ACE inhibitor treatment	5
Severe pre-existing neurological disease (severe Parkinson's disease)	1
Unknown	125
Combined confusion and ACE inhibitor treatment	1

GCS: Glasgow coma scale; ACE: angiotensin converting enzyme

Table(s)

Table 3. Demographic data on patients with chronic subdural hematomas (CSH) included for randomization in the present study	
Number of patients	248
Age (years)	75.5
Sex	173 M, 75 F
Mean size of CSH preoperatively (cm^3)	112
ACE inhibitor treatment	90
Recurrence	43

CSH: chronic subdural hematoma; ACE: angiotensin converting enzyme, M: male; F: female

Figure(s)
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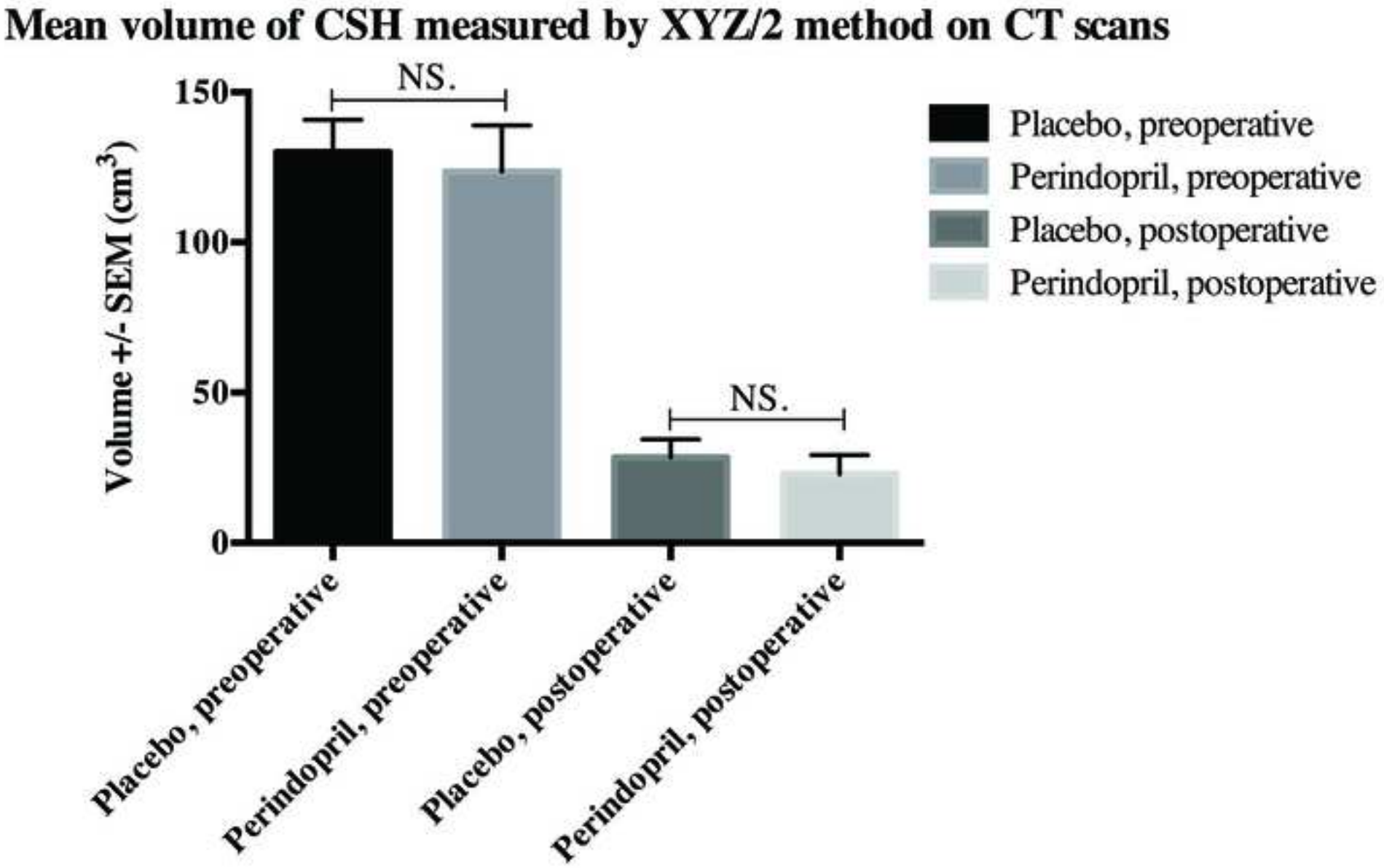

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