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ORIGINAL ARTICLE - BRAIN INJURY

COXIBRAIN: results of the prospective, randomised, phase II/III study for the selective COX-2 inhibition in chronic subdural haematoma patients

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Abstract
Background Chronic subdural haematomas (cSDHs) have shown an increasing incidence in an ageing population over the last 20 years, while unacceptable recurrence rates of up to 30 % persist. The recurrence rate of cSDH seems to be related to the excessive neoangiogenesis in the parietal membrane, which is mediated via vascular endothelial growth factor (VEGF). This is found to be elevated in the haematoma fluid and is dependent on eicosanoid/prostaglandin and thromboxane synthesis via cyclooxygenase-2 (COX-2). With this investigator-initiated trial (IIT) it was thought to diminish the recurrence rate of operated-on cSDHs by administering a selective COX-2 inhibitor (Celecoxib) over 4 weeks' time postoperatively in comparison to a control group.

Method The thesis of risk reduction of cSDH recurrence in COX-2-inhibited patients was to be determined in a prospective, randomised, two-armed, open phase-II/III study with inclusion of 180 patients over a 2-year time period in four German university hospitals. The treated- and untreated-patient data were to be analysed by Fisher's exact test (significance level of alpha, 0.05 [two-sided]).
Results After screening of 246 patients from January 2009 to April 2010, the study had to be terminated prematurely as only 23 patients (9.3 %) could be enrolled because of on-going non-steroid anti-rheumatic (NSAR) drug treatment or contraindication to Celecoxib medication. In the study population, 13 patients were treated in the control group (six women, seven men; average age 66.8 years; one adverse event (AE)/serious adverse event (SAE) needing one re-operation because of progressive cSDH (7.7 %); ten patients were treated in the treatment group (one woman, nine men; average age 64.7 years; five AEs/SAEs needing two re-operations because of one progressive cSDH and one wound infection [20 %]). Significance levels are obsolete because of insufficient patient numbers.
Conclusions The theoretical advantage of COX-2 inhibition in the recurrent cSDH could not be transferred into the treatment of German cSDH patients as 66.6 % of the patients showed strict contraindications for Celecoxib. Furthermore, 55 % of the patients were already treated with some kind of COX-2 inhibition and, nevertheless, developed cSDH. Thus, although conceptually appealing, an anti-angiogenic therapy with COX-2 inhibitors for cSDH could not be realised in this patient population due to the high prevalence of comorbidities excluding the administration of COX2 inhibitors.

Keywords Chronic subdural haematoma · Selective COX-2 inhibition · Anti-angiogenic treatment · COXIBRAIN study

The results of the COXIBRAIN study were presented at the 65th annual meeting of the German Society of Neurosurgery (DGNC), 2014

The study was registered in the European Clinical Trials Database under the Eudra-CT number 2008-000247-34

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Introduction

Chronic subdural haematoma (cSDH) is a challenging neurosurgical disease that gains more and more importance, especially in an ageing and extensive medically treated population (dialysis, anticoagulation, antiplatelet medication) [25, 26, 29]. In general, symptomatic or large cSDHs have to be treated surgically [11] as spontaneous resorption is rare. Despite optimised surgical procedure a recurrence rate of up to 20–30 % is stated [27]. With the COXIBRAIN study we aimed at clarifying the influence of selective cyclo-oxygenase-2 (COX-2) inhibition on the recurrence rate of cSDH in postoperative patients.

Study background

The incidence of cSDH varies between 2 and 13 in 100,000 individuals and rises with the average age of the population. Three-quarters of the patients are older than 50 years; the peak of incidence is at 65 years of age, with 60 % men and 40 % women patients. In the lifespan of 80–89 years of age, the incidence is even fourfold higher [1, 5, 15]. The recurrence rate is stated to be up to 20–30 %, with a mortality which is estimated to be between 1 and 13 % [21, 27, 32]. Thus, cSDH exhibits an important role in morbidity and mortality of the elderly.

In order to diminish the recurrence rate, various operative procedures were devised; an extended burr-hole trephination with drainage and irrigation, as well as the use of a Jackson-Pratt drainage is the actual preferred surgical procedure [14, 32, 33]. However, so far the pathogenesis of the subdural haematoma (SDH) and its recurrence has not been fully understood.

Inflammatory processes, osmotic gradients and a local disturbance of the haemostasis are discussed to play an important role in the development and recurrence of the SDH [7, 22, 34, 35]. The neomembranes of the SDH can be distinguished into a visceral and a highly vascularised, parietal membrane. Very thin-walled and fragile vessels can be found with numerous morphological anomalies like missing basal membranes and pericytes, cytoplasmatic protrusions and endothelial fenestrations with gap junctions of more than 8 μm in diameter. These anomalies are responsible for a higher fragility and permeability of the newly formed vessels, which probably leads to a continuous progression of the cSDH [8, 17, 18, 22, 34]. A higher concentration of growth factors, especially vascular endothelial growth factor (VEGF) can be found in the haematoma fluid in comparison to the blood serum [24, 28, 31]. VEGF is secreted by macrophages and endothelial cells in the parietal membrane [24, 30]. The excessive production of VEGF results in a precipitous neovascularisation with an increased permeability of the newly developed vessels. This might probably cause at least a persistence or even an enlargement of the SDH.

That led to the hypothesis that an inhibition of the secretion of proangiogenic mediators might be beneficial in the treatment of SDH patients [12]. The synthesis of VEGF and other proangiogenic growth factors is dependent on the COX-2-mediated eicosanoids, like prostaglandins and thromboxanes. The inhibition of the COX-2 shows anti-angiogenic and antiproliferative effects in vitro and in vivo [13, 16]. Based on this, we set out to prospectively study whether selective COX-2 inhibition might reduce the recurrence rate of cSDH.

Study design

The aim of this prospective randomised, two-arm, open, phase-II/III clinical trial in parallel group design was to verify the hypothesis of reduction of recurrence rate in cSDH by selective COX-2 inhibition for 28 days post surgical treatment. The approval of the relevant ethics committee in each study centre was obtained prior to the start of the study; each patient had to give written informed consent before being enrolled into the study.

After stratification according to gender, age and preexisting anticoagulation, patients were block-randomised in the two study treatment arms. Four study centres (university hospitals of Berlin, Mannheim, München and Greifswald) were initiated to treat 180 patients within 2 years (Fisher's exact test, power 80 % and significance level of alpha = 0.05, including a drop-out rate of 10 %).

Exclusion criteria were determined according to the contraindications of Celecoxib (Table 1). The primary target was the recurrence rate of the cSDH within 8 weeks post surgical treatment. Secondary targets comprised the time to recurrence, number of revision operations and the toxicity of treatment. One inclusion and four follow-up visits were planned postoperatively within 48 h up to the 56th postoperative day (Fig. 1).

Study execution

After the standardised surgical procedure (burr-hole trephination, haematoma drainage with a Jackson-Pratt drainage) the treatment group (B) was given 200 mg Celebrex twice daily for the first 3 postoperative days. The Celebrex dose was reduced then to 200 mg Celebrex daily for another 25 days, then discontinuation of the medication. The control group (A) did not receive any study medication and were abstained from further selective or unselective COX inhibition. The patients were followed-up for 8 weeks to evaluate the recurrence rate, the medication's side effects and the quality of life (EORTC SF 36). Because of special patient security measurements in the selective COX-2 inhibition the medication's side effects were monitored using the CTCAE

Table 1 Inclusion and exclusion criteria of the COXIBRAIN study

Inclusion criteria	1. Postoperative cSDH patients without relevant cerebral haemorrhage
	2. Age ≥18 years
	3. Karnofsky Index ≥70 %
	4. Written informed consent
	5. In fertile women: negative pregnancy testing or highly effective birth control medication
Exclusion criteria	1. Operation of an acute SDH
	2. Traumatic SDH following a severe head trauma
	3. Previous local chemotherapy or radiotherapy of the cranium
	4. Allergic reaction to sulphonamides
	5. Active peptic ulcera or gastro-intestinal bleeding
	6. Allergic reactions with asthma, acute rhinitis, nasal adenoids, angioneurotic oedema, or urticaria after use of acetylsalicylic acid or NSAR including COX-2 inhibitors
	7. Severe hepatic impairment with an albumin <25 g/l or Child-Pugh ≥10
	8. Renal impairment (creatinine clearance <30 ml/min)
	9. Inflammatory bowel disease
	10. NYHA II-IV classified heart disease
	11. Coronary heart disease
	12. Peripheral artery occlusive disease
	13. Cerebrovascular disease
	14. Active vaccination within the last 6 weeks
	15. Active hepatitis B/C
	16. Pregnancy/lactation
	17. Neurological/psychiatric disease
	18. Comatose patient without ability to consent, missing consent for data use in the analysis of the study
	19. Participation in another clinical trial within the last 4 weeks
	21. Pre-existing medication with (non-)selective COX-2 inhibitors

version 3.0 in the five study visits. The results were prospectively monitored with the use of the Bayesian toxicity assessment and discussed in the external Data Safety Monitoring Board.

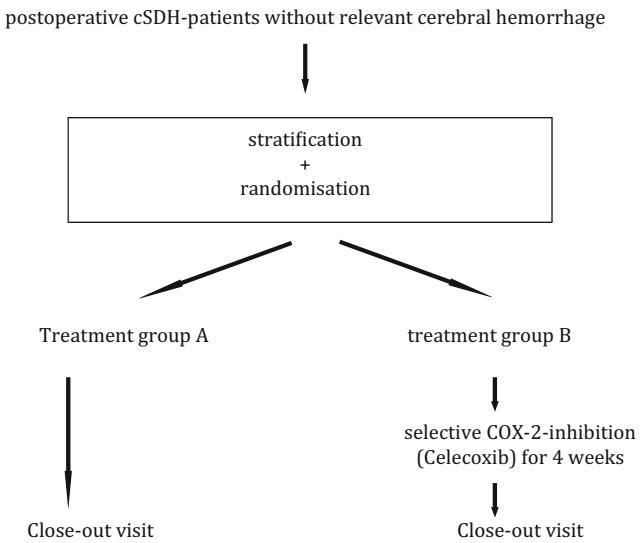

Fig. 1 COXIBRAIN study overview

Patient characteristics

Twenty-three patients were enrolled before the trial was discontinued because of an insufficient study inclusion rate. Out of 23 patients, 13 were randomly assigned to the control group (A) and 10 patients to the treatment group (B). The control group (A) consisted of seven men (53.8 %) and six women (46.2 %) patients with the mean age of 71 years, whereas treatment group (B) consisted of nine men (90 %) and one woman patient (10 %) with the mean age of 65 years. The overall the study population consisted of 16 men (69.5 %) and seven women (30.5 %) patients with the mean age of 68 years.

Study discontinuation

The COXIBRAIN study was initiated on 1 January 2009 and closed prematurely on 28 April 2010 because of insufficient patient inclusion rates. Two hundred and forty-six (178 male [72 %] and 68 [28 %]) female patients were screened but only 23 were suitable to be enrolled into the study mainly because of contraindications to selective COX-2 inhibition (163 patients [67 %]) or pre-existing therapy with antiplatelet medication (pre-existing COX inhibition in 135 patients [55 %]). Forty patients refused to participate in this study. This added up to a patient inclusion rate of just 9.4 % to the trial.

Nearly two-thirds of the screened patients (163 patients) showed a contraindication for treatment with Celebrex (e.g. cardiopulmonary contraindication like NYHA II-IV or coronary diseases). This is equal to a 2.3-fold increase in contraindications for COX-2 inhibition in comparison to the total patient collective at the Charité hospital of 28.4 % in 2009/2010. A pre-existing medication with (non-)selective cyclo-oxygenase inhibitors was determined in 55.5 % of the screened patients (135 patients) (Fig. 2).

Results

No patient showed a recurrence of the cSDH with the need of reoperation within the follow-up time of 8 weeks. After a prolonged follow-up time of 2 years, one patient with recurring cSDH (7.7 %, occurrence 9 months postoperatively) had to be operated on in the control group (A), as well as one patient with cSDH in the treatment group (B) (10 %, occurrence 6 months postoperatively).

In the control group (A), one serious adverse event (SAE) was noted. One patient suffered from prolonged nausea and vomiting;

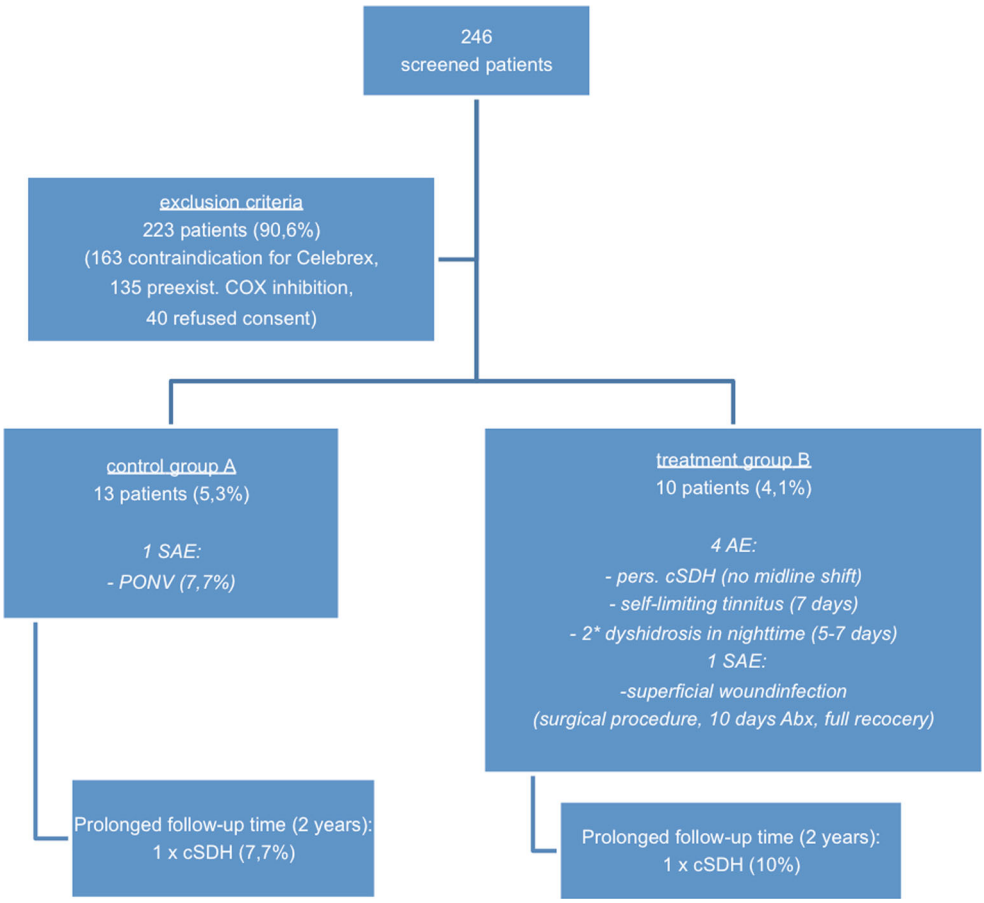

Fig. 2 COXIBRAIN study patient flow chart

which led to a prolonged hospital stay; a definite discrimination to postoperative nausea and vomiting (PONV) could not be achieved.

In the treatment group (B), five events (four AEs and one SAE) occurred. Of the four AEs, one patient showed a persisting cSDH albeit with regression of the midline shift. One patient complained about self-limiting tinnitus after 7 days. Two patients experienced self-limiting dyshidrosis in the night-time for 5-7 days without elevation of the body temperature. The SAE was a superficial wound infection including one surgical procedure, followed by 10 days of antibiotic therapy, with full recovery of the patient.

Because of the low numbers of patients significance concerning the primary or secondary endpoints could not be retrieved.

Discussion

The COXIBRAIN study was closed early because of the insufficient study inclusion rate of patients. In the pre-study, the elevated number of contraindications in cSDH patients and the number of patients under antiplatelet therapy in the patient collective were, unfortunately, not obvious.

In cSDH patients, the probability of anticoagulation with unselective cyclo-oxygenase is highly increased. This is most likely related to an elevated odds ratio (OR) of 1.4 for development of a cSDH in patients with antiplatelet therapy (OR 4.3 for spontaneous cSDH development under antiplatelet therapy, whereas OR 1.7 for the development of cSDH in trauma patients under antiplatelet therapy) [4]. Additionally, a relevant group of patients was not eligible for the study because of the strict contraindications to Celecoxib (e.g. coronary heart disease, heart insufficiency, peripheral arterial occlusion, cerebrovascular diseases and neurological/psychiatric diseases). Patients with a cSDH show a high percentage of at least one of the above-mentioned contraindications.

In several neoplastic diseases (like mamma carcinoma, chondrosarcoma and glioblastoma multiforme), increased COX-2 expression was demonstrated [3, 20, 23]. Several clinical trials showed a decrease in tumour progression via an inhibition of the angiogenesis [9, 10, 16].

So COX-2 inhibition might lead in cSDH patients to a decelerated and thus reduced angiogenesis. Therefore, it may be an appropriate treatment in selected patients as the treatment group

did not show an increased morbidity or mortality (as long as the low numbers of patients are representative).

Conclusions

Although conceptually appealing, an anti-angiogenic therapy of COX-2 inhibitors for cSDH could not be realised in this patient population due to the high prevalence of comorbidities excluding the administration of COX-2 inhibitors or the pre-existence of selective or unselective COX inhibition.

In the literature, alternative treatment approaches to diminish the recurrence rate of cSDH dominate now. Trials with intraoperatively applied tissue plasminogen activator (TPA) [19], perioperative application of corticoids [2] or an altered regiment of postoperative anticoagulation [6] show promising results but have to be executed on a larger scale.

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Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

Disclosure The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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