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

Abstract:

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 cyclo-oxygenase-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. 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]). 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. 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.

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