Acta Neurochir (2016) 158:2045–2046
DOI 10.1007/s00701-016-2950-x

EDITORIAL (BY INVITATION)

Clinical trials: do we need criteria for pre-study feasibility assessment?

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Received: 24 August 2016 / Accepted: 25 August 2016 / Published online: 7 September 2016

In this issue of Acta Neurochirurgica, Schaumann et al. [1] report on the experiences and absence of results in the COXIBRAIN study on patients with chronic subdural hematoma. COXIBRAIN was designed as a prospective randomized nonblinded phase II/III study to investigate the efficacy of COX-2-inhibition for preventing recurrence rates following surgery of patients with a chronic subdural hematoma. The concept that COX-2-inhibition may reduce inflammatory responses and in particular inhibit the secretion of proangiogenic mediators in the subdural space is of interest and supported by experimental evidence. Recurrence rates are substantial in patients following surgery for a cSDH and have been reported in up to 20–30 % of procedures. Standard surgical approaches to limit recurrence rates consist of copious irrigation and a postoperative drain in the subdural space. Obtaining a further reduction in recurrence rates following surgery would be highly relevant to clinical practice. Unfortunately, this trial was terminated prematurely due to low recruitment, caused by the fact that exclusion criteria were present in many patients screened. Over a 14-month period, only 23 patients could be recruited out of a potential of 246. Meaningful conclusions could therefore not be drawn. Nevertheless, this publication should be considered important for two main reasons.

First, it is important that 'negative' trials are reported and the reasons for failure of the study shared with other investigators. The study was designed according to state-of-the art practice and registered in the European Clinical Trials Database. A relative limitation was that the study was not designed as a double-blinded study, for the simple reason that the costs of manufacturing identical placebo solutions could not be afforded within this investigator-initiated trial. This sends an important message to funding organizations: investigator-initiated studies should be supported to an extent that permits generation of scientific evidence of the highest quality.

Second, a pre-initiation rigorous feasibility study might have revealed the risk of low recruitment due to a large number of exclusions. The main reasons for exclusion in this study were contra-indications to selective COX-2-inhibitors ($n = 163$), and pre-existing therapy with antiplatelet medication ($n = 135$). Rigorous evaluation of patient potential during the design phase of the study might have revealed the fact that many patients would not meet enrolment criteria. This highlights the necessity for rigorous pre-study evaluation of not only the evidence in support of the intervention but also of patient potential in terms of population studied (number of patients meeting enrolment criteria) and site caseload (how many patients potentially available per site).

Looking back is always easy and a retrospectroscope is a handy instrument. However, good science includes a critical evaluation of successes and failures and every failure has the potential to improve the next study. In this case, the main message is to highlight the importance of pre-study feasibility evaluations. From this perspective, we reviewed the study protocol registered under number 2008-000247-34 in the European Clinical Trials Database, and found no mention of feasibility assessment. On review of the standard registration forms for trials in the US trial registry (clinicaltrials.gov), similarly no information is requested on feasibility assessments. The rigor with which experimental data and results from phase II studies should be evaluated prior to proceeding to a phase III study is well recognized. We suggest that pre-study feasibility evaluations may be equally relevant.

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The authors of COXIBRAIN should be congratulated on sharing their experiences of this failed trial with the scientific community and the editors of this journal deserve our compliments, for not only accepting this manuscript, but also for providing the opportunity to highlight it in an editorial. It is highly important that the results of "negative" studies are reported!

References

1. Schaumann A, Klene W, Rosenstengel C, Ringel F, Tüttenberg J, Vajkoczy P (2016) COXIBRAIN: results of the prospective randomized, phase II/III study for the selective COX-2- inhibition in chronic subdural hematoma patients. Acta Neurochir. doi:10.1007/s00701-016-2949-3