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WHAT'S NEW IN INTENSIVE CARE

The Boldt scandal still in need of action: the example of colloids 10 years after initial suspicion of fraud

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Introduction

Dr Boldt had a prolific publication record of randomized clinical trials when readers questioned the authenticity of a study comparing albumin and hydroxyethyl starch (HES) for cardiopulmonary bypass priming published in *Anesthesia & Analgesia* in December 2009 [1]. For the investigator-initiated study it turned out that there was no institutional review board (IRB) approval, no written informed consent of patients, and patient or laboratory data were missing; effects of albumin in bypass priming were described, although the hospital had not been providing albumin solutions for cardiac surgery since 1999 [2]. The data of this publication had been fabricated, and the notice of retraction was published in 2010 [3]. In the subsequent investigation, the medical authority responsible for the City Hospital of Ludwigshafen, Germany was unable to verify IRB approvals for a total of 88 publications on single-center clinical studies performed at Dr Boldt's new workplace in Ludwigshafen after he had left the University Hospital of Giessen in 1996 [2]. In March 2011, editors of 18 journals announced their intention to publish formal retraction notes to the 88 papers in each journal [4]. Additionally, two of the retracted publications were probably falsified as well since human albumin used in cardiac surgery patients reported here in fact was not available in the hospital for this indication [5, 6]. With regard to studies published from 1984 to 1998, ethical issues and possible fraud by Dr Boldt remain unclear because IRB documentation was checked only for studies published from 1999 onwards.

From missing institutional review board approvals to scientific fraud

According to the Ludwigshafen City Hospital, at least 10 of 91 evaluated studies published after 1999 included false data; however, details of the investigation carried out by Dr Boldt's employers were not made public [4]. Therefore, apart from serious breaches of professional ethical conduct, it is not unreasonable to raise doubts regarding the fraudulent nature of papers not yet retracted. Suspicion of fraud is also supported by evidence of a different kind. In his analysis of 79 randomized trials published with Boldt as an author, John Carlisle, an editor of *Anaesthesia*, identified non-random sampling, raising the suspicion that data fabrication was the reason; 44 of these studies had been retracted until 2013. Of the 35 studies not retracted, 10 displayed aberrant statistical characteristics that "undermine the assumption that they are genuine" (in comparison with 13/44 retracted studies) [7]. As early as 2006, the fluid sepsis studies of Boldt were investigated using a similar method of analysis, and irregularities were identified and published [8].

Search for falsification in the entire set of trial publications by Dr Boldt is still ongoing. Nearly 40% of clinical trials were carried out at the University Hospital Giessen, and articles based on these trials were published prior to 1999. From comparisons between doctoral theses and corresponding papers, there is evidence of data falsification of publications. It can reasonably be assumed that large-scale fraud probably occurred also in Giessen [9].

After the editors' announcement in 2011, investigations by the author's institution in Giessen, third parties, and journals have identified evidence of data fabrication,

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falsification, and other types of manipulation in eight more publications, leading to a total of 96 retractions until 8 June 2018 (http://retractiondatabase.org/). On the basis of a confidential communication from the University of Giessen to the editors of the journals involved, from which "Retraction Watch" was permitted to quote in 2015, several additional publications by Boldt are assumed to be falsified [10, 11]; however, a final report from Giessen is still awaited, and fraudulent publications remain active with the whole potential of harm to patients and science.

Impact of Boldt publications on evidence base for colloids in volume resuscitation

Inclusion of data from studies by Boldt and coworkers had strongly influenced the results of meta-analyses. In Zarychanski et al. [12], no association between HES and all-cause mortality was found when seven studies conducted by Boldt et al. in the 1990s that had not yet been retracted were included. However, HES was found to be associated with a significantly increased risk of mortality after these studies were excluded.

Updating the fate of publications on volume therapy with colloids, PubMed listed entries with "Boldt" as an author and "hydroxyethyl" starch or human "albumin" solutions as title/abstract query terms have been searched and analyzed. Methods are available as electronic supplementary material and results summarized in Fig. 1.

Forty-four publications were found, all reporting single-center studies mostly involving only his or his and one additional department. Typically, no information was given when study patients were recruited. Boldt served as lead author on about two-thirds of these publications; for two-thirds, the University Hospital of Giessen is the responsible institution. On 7 June 2018, 20 PubMed entries (45.4%) had published retraction notices. At least nine of the 20 retracted publications reporting randomized trials contained falsified data, three being from the time period when Dr Boldt was working in Ludwigshafen, and six when he was in Giessen. Among these six publications, one was his first fraudulent paper published in 1986. Thus, unethical publishing presumably dates back to Dr Boldt's very early years as a clinical scientist and not yet specialized as an anesthetist, and then continued during his entire career. Theoretically, scientific malpractice could have been uncovered much earlier than 2009. As early as 2004, because of the suspicion of unethical conduct of trials, an official investigation of Dr Boldt, Dr Hempelmann, the former director of Dr Boldt's Department of Anesthesiology and Surgical Intensive Care and a co-author of about 180 PubMed-listed publications, and others from the University of Giessen was initiated but stopped because of insufficient evidence of unethical scientific practice. The ties between the University Department and the German HES-producing industry appeared to be close [13].

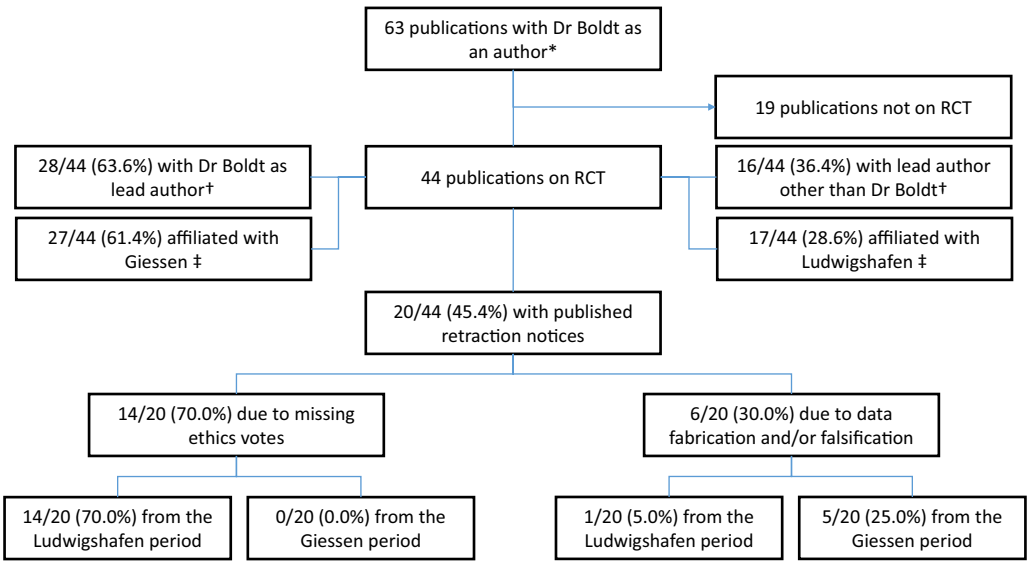

Fig. 1 Flowchart of the fate of 44 publications of randomized clinical studies on volume therapy with colloids with Boldt as an author. *Additional search terms were "hydroxyethyl" or "albumin" in title/abstract and search performed on June 7, 2018. ‡Studies at the University of Giessen and Ludwigshafen were between 1985 and 1998 (mean annual RCT rate, 1.93) and from 1999 to 2010 (mean annual RCT rate, 1.42), respectively. †Lead author = first, senior, or corresponding author

Conclusions

Type and history of fraud confirm that Dr Boldt falsified clinical data during his entire career. Many clinical trial publications have been retracted but more retractions can be expected if stakeholders work together. "Burden of proof reversal" could well be an option and, hence, all papers with Boldt as lead author can be retracted; alternatively, all unretracted papers could be marked with the label "expression of concern" [9], at the very least. There are many open questions regarding institutional, editors', and publishers' responsibilities. A simple calculation of his clinical trial output should have raised concerns as it is almost impossible to carry out more than 200 single-center clinical trials, many of these done at a city hospital with fewer resources than a university hospital, with thousands of patients, with more than 180 co-authors (CJ Wiedermann, unpublished), over a period of just 25 years. It is surprising then that no suspicion of misconduct arose during this period in either of the two institutions where he worked. However, both journals and publishers still seem reluctant to publish notes of retraction [14]. Considering the evidence and magnitude of this fraud, one is left wondering how much more evidence is needed before journals are prepared to publish retractions.

COPE guidelines (https://publicationethics.org/resources/guidelines) to detect fraud and retract questionable publications need to be enforced by the parties involved. Finally, there is an unmet need for methods of computerized identification of falsification such as testing for non-random sampling [15] which should be further investigated.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5289-3) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

CJW has received lecture fees and/or travel cost reimbursements from the Plasma Protein Therapeutics Association, Kedrion, CSL Behring, Grifols and Baxter, and remuneration for consulting from CSL Behring, Grifols, and Daiichi Sankyo. MJ has received fees for lectures and/or consulting from Baxter, CSL Behring, Fresenius and Astute Medical, and research grand support from Fresenius.

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