Authors' Reply

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In our study [1], the primary end point referred to hemodynamic parameters, more specifically to cardiac output and its changes from baseline during 24 h. Power analysis and computation of the number of patients needed referred to the hemodynamic parameters. The safety parameters were secondary efficacy variables. This was clearly stated by us in the Materials and Methods section.

To investigate possible effects on the coagulation system, indeed only a relatively small number of patients is needed, because the pathomechanism of coagulation disorders caused by hydroxyethyl starch (HES) is by and large understood. Treib [2], Baron and Treib [3], and Treib et al. [4–6] were able to show through extensive studies, some of which were quoted by Wiedermann, that

the effects on the coagulation system are the larger, the higher the molecular weight and particularly the degree of substitution of HES. For this reason, no clinically relevant coagulation problems were to be expected for HES 130/0.4. However, this has not been explicitly studied yet, so that we were able to show this for the first time in vivo. Our earlier studies showed that the number of patients investigated by us is entirely sufficient for this particular question. According to our results, HES 130/0.4 shows no clinically relevant effect on the coagulation when compared with electrolyte solution, contrary to the more highly substituted HES solutions studied by us. In this context, HES 130/0.4 can be considered a safe solution, and we consider this statement to be justified and

correct, particularly in a journal that deals frequently with all scientific aspects of coagulation.

Regarding the question of side effects such as pruritus, a higher number of patients is needed to make valid statements, since these side effects are rare. As discussed above, this was a secondary criterion. To our knowledge, no valid data from a randomized, prospective study exist, in which HES in general or HES 130/0.4 was administered for several days to a larger number of patients and which investigated specific side effects such as pruritus. A study performed by Kimme et al. [7] investigated retrospectively 44 patients who had received HES at varying doses (cumulative doses showed a wide range from 500 to 19,500 ml) as hemo-

Table 1. Results of baseline examination and difference between baseline examination and examination after 96 h

	Baseline examination		Mean pre-post difference between baseline examination at 0 h and examination after 96 h	
	HES (ITT)	electrolyte solution	HES (ITT)	electrolyte solution
Platelets, $\times 10^9/l$	260,450 $\pm$ 57,876	233,300 $\pm$ 54,832	–24,150 $\pm$ 30,983	–11,368 $\pm$ 22,184
PT, %	97.25 $\pm$ 4.47	98.0 $\pm$ 4.41	–0.58 $\pm$ 5.10	–0.44 $\pm$ 3.70
aPTT, s	29.40 $\pm$ 2.74	29.30 $\pm$ 1.69	+0.84 $\pm$ 2.22	+0.28 $\pm$ 3.77
Fibronectin, mg/dl	36.62 $\pm$ 7.58	44.32 $\pm$ 20.02	–2.47 $\pm$ 7.27	–4.67 $\pm$ 18.59
Factor VIII:C, %	92.89 $\pm$ 36.38	103.26 $\pm$ 34.60	–9.37 $\pm$ 32.11	–10.32 $\pm$ 26.49
vWF:Ag, %	126.53 $\pm$ 31.88	126.28 $\pm$ 26.37	–10.95 $\pm$ 15.14	+8.79 $\pm$ 18.41
vWF:RCoF, %	96.16 $\pm$ 39.80	116.63 $\pm$ 50.25	+0.37 $\pm$ 30.28	+3.11 $\pm$ 34.28

PT = Prothrombin time; aPTT = activated partial thromboplastin time; vWF = von Willebrand factor.

dilution therapy after subarachnoid hemorrhage. There was significantly more pruritus in patients who received more than 5,000 ml of HES versus those who received less than 5,000 ml. Our data suggest that the problem does not exist to the extent suspected by Kimme et al. [7] in the HES 130/0.4 investigated by us. These authors overestimated the problem in a study with the same number of subjects, but less sophisticated methods. We agree with Wiedermann that, regarding the question of pruritus and HES, a prospective study with a large patient sample would be desirable.

The data about coagulation and particularly factor VIII/von Willebrand factor were omitted by us for reasons of space, since they showed no relevant changes. We would be happy to supply these data in table 1. Concerning possible influences through the sponsor of the study, we would like to underline that the sponsor at no point had any illegitimate influence on the collection, analysis, or interpretation of the data or on the writing of the manuscript. We would like to point to the last sentence of our manuscript, discussing the primary parameter hemodynamics: 'However, HES 130/0.4 was not superior to crystalloid solution regarding the therapeutic effect on systemic and cerebral perfusion during continuous infusion' [1]. In our mind, such a statement speaks for itself and shows no undue influence of the sponsor.

Regarding the question of efficacy and usefulness of the administration of HES during acute stroke, the data are contradictory. The goal of our study was not to study the efficacy of HES in the therapy of acute stroke – for this, the patient sample is indeed too small. However, several of the studies quoted by Wiedermann are very old and have from today's perspective a time window for inclusion that is unacceptable. The

newest (pilot) study about this question performed by Rudolf and colleagues [8] showed in a relatively small patient sample of 106 patients with acute ischemic stroke a trend towards a better functional outcome with HES therapy.

We do not agree with the comment by Wiedermann about the quantity of HES or crystalloid solution infused. A cumulative dose of 6,500 ml HES over 4 days is a large quantity, particularly in comparison with other studies and clinical routine. Especially regarding a 'dose dependency for the incidence of HES-induced pruritus', reported by Kimme et al. [8], a dose of 6,500 ml over 4 days is rather high.

In sum, our study was able to show that no significant differences were observed regarding the primary criterion cardiac output between HES 130/0.4 and crystalloid solution. The question of side effects of HES should be investigated in a special prospective study with a large patient sample.

Over the last 10 years, our group has carried out a large number of studies investigating the effects of various types of HES at different concentrations and therapy durations. While it is easy to demand larger studies with ever more statistical power, Wiedermann, like any physician, must be aware of the feasibility and cost of these studies. Naturally, it would be always desirable to have more and more studies with larger and larger patient samples. This is true for all branches of medicine. However, we think, it is unethical and from a scientific perspective not productive to not carry out studies at all because of possible (or imagined) limitations. This way, no progress towards better therapies and an enhanced understanding of pathophysiology is made, and important knowledge is withheld from physicians and ultimately from patients.

References

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