DOI: 10.1161/STROKEAHA.121.038455

Analyses of the Primary Outcome

The adjusted absolute treatment effect of IVF to achieve a favorable functional outcome at 6 months using the entire IPD-cohort(n=1,501) was 9.3%,95%CI(4.4-14.1),p<0.001, according to the most conservative model identified by sensitivity analyses(all models, ATE-range:9.3-10.0%,**TableS8**). The adjusted-OR to achieve favorable functional outcome was 1.69,95%CI(1.26-2.23),p<0.001;(e-values, point-estimate:1.92, confidence-interval:1.50) and the crude difference for the entire cohort(n=1.501) was 42.1%(251/596) vs 30.5%(276/905). Graphical representation of the mRS distribution at 6 months using the propensity matched cohort(n=1,150) is shown in **Figure2A,** with a difference in proportions of favorable functional outcome of 42.4%(244/575) vs 35.0%(201/575), for sensitivity analyses of the propensity-matched cohort(**TableS9,FigureS5**).

Analyses of Secondary Outcomes

IVF treatment was associated with a significant shift towards improved functional outcome across the entire range of mRS, common-OR:1.75,95%CI(1.39-2.17),p<0.001;(e-values, point-estimate:1.98, confidence-interval:1.64). Mortality at 6 months was significantly reduced with IVF treatment compared to SoC, adjusted-OR:0.47,95%CI(0.35-0.64),p<0.001;(e-values, point-estimate:2.28, confidence-interval:1.81), with an ATE:-10.0%,95%CI(-14.5--5.4),p<0.001. Focusing on safety **Figure2B** provides an overview of evaluated adverse events. In total 14.9%(89/596) adverse events in IVF treated patients were detected compared to 13.5%(122/905) in patients who received SoC, with an adjusted AD:1.0%,95%CI(-2.7-4.8). New intracranial hemorrhagic complications were present in 8.6%(51/596) of IVF treated patients compared to 6.0%(54/905), a difference that was not statistically different, with an adjusted AD:0.8%,95%CI(-2.3-3.0);**TableS10**.

Exploratory Sub-group Analyses

For associations of IVF with the primary outcome(**Figure3**), significant ATE were found in younger patients aged 23-55yrs,ATE:13.4%,95%CI(5.5-21.3), in patients with lower GCS(3-7)values,ATE:12.1%,95%CI(5.0-19.3), in non-deep ICH,ATE:10.4%,95%CI(0.8-23.1), or non-thalamic ICH,ATE:12.6%,95%CI(5.4-19.8), as well as in patients with larger ICH-volumes(≥19.2ml),ATE:10.9%,95%CI(2.8-19.0), and moderate IVH-volumes(16.0-33.3ml), ATE:10.6%,95%CI(3.0-18.2). The largest ATE was observed for symptom onset to

DOI: 10.1161/STROKEAHA.121.038455

treatment, especially in the earliest time-window(treatment started within first tertile<29.9hours after onset),ATE:23.0%,95%CI(12.8-33.2). The following time-window(29.9-52.8hours) remained significantly associated but revealed a lower ATE:10.0%,95%CI(1.3-18.7). Significant interactions between treatment and sub-group categories were not detected, all p>0.05. Similar associations were appreciated for the secondary outcomes(ordinal-shift analysis, mortality and adverse events,**TablesS11-13**). Early IVF treatment(<29.9 hours) was associated with the largest shift towards improved functional outcomes, common-OR:2.70,95%CI(1.67-4.35). Mortality reduction was most distinct in patients with GCS(3-7)values,ATE:-19.6%,95%CI(-26.9--12.2), and larger ICH-volumes(≥19.2 ml)ATE:-19.3%,95%CI(-28.2--10.3). Upon exploratory analyses of IVF treatment with adverse events the only significant association was observed in patients with thalamic ICH, adjusted-OR:1.74,95%CI(1.04-2.93),p=0.04(**TablesS11-13**).

Threshold Analyses for the Primary Outcome

Exploratory threshold-analysis of treatment effect modifiers with the primary outcome showed significant treatment effects of IVF almost across the entire range of age and GCS-levels(**FigureS6A+B**) as well as for patients with intermediate-sized ICH(above 8-67ml) and IVH(above 12-69ml)-volumes(**FigureS6C+D**). The most clear-cut threshold for treatment effects associated with favorable functional outcome was identified for the predictor: time from symptom onset to initiation of IVF treatment(**Figure4**). Translating this threshold(IVF-treatment received≤ 48 hours compared to SoC) resulted in an ATE of 15.2%,95%CI(8.6-21.8),p<0.001, to achieve the primary outcome(for the entire cohort analysis 78.5%(1,179/1,501) of patients were analyzed within the 48 hour time-frame). Validating this time-window threshold exclusively with CLEAR trial data resulted in an ATE of 13.3%,95%CI(3.3-23.4),p=0.009 to achieve favorable functional outcome(for the CLEAR trial cohort analysis 68.4% (366/535) of patients were analyzed within the 48 hour time-frame).

DOI: 10.1161/STROKEAHA.121.038455

DISCUSSION

The present IPD meta-analysis incorporated trial- and observational-data and represents the largest analysis of patients treated with IVF to date. We provide that the use of IVF in this pooled analysis of 9 studies was related to improved functional outcome, specifically in an early time window <48hours with an effect-size of 15% using the IPD-cohort, which was validated using only CLEAR trial-data(effect-size:13%). Further, we extend prior observations that the intervention is safe, feasible, and was significantly associated with improved survival.

What may be the reason that this analysis provided positive associations while a trial showed neutral results on functional outcome? Possible explanations refer to differences in patient selection and treatment characteristics among observational- compared to trial-data. In observational studies patient selection was most likely based upon expertise and individual protocols. A priori selection bias was rigorously addressed by sophisticated statistical means in this current study, yet important differences in patient selection compared to trial data were apparent. The latter involved more patients with thalamic ICH(59% vs 46%), a location with worse prognosis[6]. Trial inclusion criteria lead to significantly less patients treated with larger ICH-volumes(≥19.2ml) compared to non-trial patients(14% vs 44%) potentially associated with our results. Specifically, as IVF treatment in these patients provided robust associations with reduced mortality(ATE:19%) and increased favorable outcome(ATE:11%). One general question refers to the conflict between internal vs external validity of RCTs[32]. CLEAR-III was aimed at addressing both as large international multicenter trial recruiting patients from 73 sites in 8 countries[3]. Yet, IVF represents a technical strategy disruptive to usual clinical practice and therefore not always fully applied in each clinical situation. We have learned from various randomized trials, e.g. mechanical thrombectomy or carotid endarterectomy in ischemic stroke, that hallmarks are crucial to demonstrate a clinical net-benefit, such as patient selection, experience, and timing[33]. Similarly, our data suggests optimized patient selection, possibly higher center-experience, and most strikingly identified time from symptom onset to IVF as therapeutic window for treatment benefit up to 48 hours.

This hypothesis generating analysis provides background evidence to justify exploring new questions. What may be the mechanistic concept behind rapid IVH-resolution benefitting patients? Severe IVH leads to mass

effect on ependymal-, midbrain-, and brainstem structures, along with obstructive hydrocephalus leading to direct damage and global brain hypoperfusion[34,35]. In various studies IVH appears to exert independent effects on outcome beyond ICH-volume. Acute injury may be related to exaggerated neuroinflammation, yet causal relationships between outcome and acute inflammation, disturbed autoregulation, and the glymphatic system need to be determined[36,37]. Rapid clot removal by IVF limits exposure to blood-related toxins and harbors the potential to improve pathophysiology. However, IVF is not modifying parenchymal lesions suggesting that functional benefit may be driven by similar mechanisms influencing survival or otherwise by unknown factors which need to be elucidated. Specific analyses of CLEAR-III control group data suggest that instillation of saline only, i.e. mechanical clot manipulation, neither led to rapid IVH resolution nor to a time-dependent association on clinical outcomes[3]. Hence, rapid clot removal achieved by alteplase is linked to improved functional outcome, presumably by multifactorial mechanisms stated above in a time-dependent manner. Regarding a subsequent randomized trial design, our findings support the evolving belief that “time is brain” not only in ischemic stroke. Current ICH trials have started to target early time-windows(NCT03385928,NCT03209258,NCT04434807)[38]. Although time scales for ICH may be different than for ischemic stroke, our data suggest that early treatment with IVF is safe, feasible, and may positively influence outcomes.

Our results should be cautiously understood within the context of limitations pertaining to observational data(selection bias) from multiple cohorts as only 2 of 9 studies represented trials. Moreover, all observational studies were conducted by academic centers located in the USA and Germany with specialized neuro-intensive care units. The generalizability to hospitals without such capability is not addressed, but this may represent a potential avenue for quality improvement and implementation research. This study represents by far the largest investigation, tripling the size of the CLEAR-III, yet random sequence generation and allocation concealment was largely not present. Data derived from multiple cohorts required data harmonization to increase inferential equivalence[26]. Bias due to confounding was addressed by robust statistical methodologies and sensitivity analyses included unmeasured confounding, yet may not have completely compensated for this bias. Patients included into this study spanned a time-frame from 2004 to 2016 with potential adaptations of ICH-management. Imaging analysis was not centralized and lesion volume evaluation used validated but not

standardized methodologies across all patients, which may have resulted in over- or under-estimation. In addition, outcome was scored according to individual study protocols and may have been influenced by variability in time-point estimation or assessment methodology. We up-dated our systematic review search at 25/05/21, which resulted in one more cohort study eligible for inclusion with a sample size of 80 patients representing a theoretical increase of 5% to the current investigation and therefore omission was considered sensible[39].

Conclusions

As compared to SoC, the administration of IVF in patients with intracerebral and intraventricular hemorrhage was significantly associated with improved functional outcome at 6 months. The treatment effect was linked to an early time-window<48h, specifying a target population for future trials.

Sources of Funding

This work was partly supported by research grants from the Johannes & Frieda-Marohn Foundation (FWN/Zo-Hutt/2011) and from the ELAN fonds(ELAN 12.01.04.1), University of Erlangen, Germany; the Jeffrey and Harriet Legum Professorship in Acute Neurological Medicine at Johns Hopkins University; and grants from the U.S. National Institutes of Health (NINDSU01NS080824; NCATSU24TR001609). M.E. received funding from DFG under Germany´s Excellence Strategy–EXC-2049–390688087,BMBF,DZNE,DZHK,EU,Corona Foundation, and Fondation Leducq.

Role of funder

The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures:

None of the authors report conflicts of interest related to the contents of the manuscript. Outside the submitted work the following authors reported conflicts of interests: Dr Kuramatsu reports compensation from Biogen

Idec for other services and grants from Alexion Pharmaceuticals. Dr Ziai reports compensation from BARD for consultant services and compensation from Neurocritical Care Society for consultant services. Dr Selim reports grants from NIH/NIA; grants from NIH/NINDS; and compensation from MedRhythms,Inc for consultant services. Dr Lioutas reports compensation from Qmetis for consultant services. Dr Endres reports compensation from Amgen for other services; compensation from Pfizer for other services; compensation from Daiichi Sankyo Company for other services; compensation from Bristol-Myers Squibb for other services; grants from Bayer Healthcare; compensation from AstraZeneca for other services; compensation from Bayer Healthcare for other services; compensation from Boehringer Ingelheim for other services; compensation from Novartis for other services; compensation from SANOFI-AVENTIS U.S. LLC for other services; and grants from Deutsche Forschungsgemeinschaft. Dr Ringleb reports travel support from Bayer Healthcare; compensation from Boehringer Ingelheim for consultant services; travel support from Bristol-Myers Squibb; and compensation from Daiichi Sankyo Company for consultant services. Dr Erbguth reports grants from Boehringer Ingelheim. Dr Schellinger reports compensation from AstraZeneca for consultant services; compensation from Bayer Healthcare for consultant services; compensation from Daiichi Sankyo Europe GmbH for consultant services; compensation from Boehringer Ingelheim for consultant services; and compensation from Bristol-Myers Squibb for consultant services. Dr Röther reports compensation from AstraZeneca for consultant services and compensation from AstraZeneca for other services. Dr Günther reports compensation from PFIZER PHARMA GMBH for other services; compensation from Ipsen Pharma SAS for other services; compensation from Daiichi Sankyo Company for other services; and compensation from Boehringer Ingelheim for other services. Dr Testai reports grants from National Institutes of Health. Dr Alexandrov reports compensation from Genentech, Inc. for other services; compensation from AstraZeneca for consultant services; and employment by Health Science Center, University of Tennessee. Dr Sheth reports grants from Hyperfine; compensation from ZOLL Medical Corporation for data and safety monitoring services; compensation from CSL Behring for consultant services; grants from Novartis; compensation from Cerevasc for consultant services; a patent pending for Stroke wearables licensed to Alva Health; grants from Biogen; compensation from Rhaeos for consultant services; service as President for Advanced Innovation in Medicine; compensation from Sense for data and safety monitoring services; compensation from Certus for consultant services; and grants from BARD. Dr Awad reports grants from NIH/NINDS, compensation from Medicoegal consulting for expert witness services;

compensation from Neurelis, Inc. for consultant services; and grants from Stridebio. Dr Hanley reports grants from National Institute of Neurological Disorders and Stroke; gifts from Jeffrey and Harriet Legum Professorship in Acute Neurological Medicine at Johns Hopkins University; and grants from National Center for Advancing Translational Sciences. Dr. Huttner reports compensation from Boehringer Ingelheim for consultant services.

Data Access, Responsibility, and Analysis

Dr. Kuramatsu and Dr. Huttner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supplemental Materials

Supplemental Methods Systematic review and statistical analysis plan

Tables S1-13

Figures S1-6

PRISMA-IPD Checklist

References[40-42]

Appendix

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