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Association of intraventricular fibrinolysis with clinical outcomes in ICH: an individual participant data meta-analysis

Joji B. Kuramatsu[1,+], MD; Stefan T. Gerner[1,+], MD; Wendy Ziai[2,+], MD; Jürgen Bardutzky[3,], MD; Jochen A. Sembill[1], MD; Maximilian I. Sprügel[1], MD; Anne Mrochen[1], MD; Kathrin Kölbl[1], MD; Malathi Ram[2], PhD, Radhika Avadhani, MS[2], Guido J. Falcone[4,5], MD; Magdy H. Selim[6], MD; Vasileios-Arsenios Lioutas[6], MD; Matthias Endres[7-10], MD; Sarah Zweynert[7], MD; Peter Vajkoczy[11], MD; Peter A. Ringleb[12], MD; Jan C. Purrucker[12], MD; Jens Volkmann[13], MD; Hermann Neugebauer[13,14], MD; Frank Erbguth[15], MD; Peter D. Schellinger[16], MD; Ulrich J. Knappe[17], MD; Gereon R. Fink[18], MD; Christian Dohmen[18,19], MD; Jens Minnerup[20], MD; Heinz Reichmann[21], MD; Hauke Schneider[21,22], MD; Joachim Röther[23], MD; Gernot Reimann[24], MD; Michael Schwarz[24], MD; Hansjörg Bäzner[25], MD; Joseph Claßen[26], MD; Dominik Michalski[26], MD; Otto W. Witte[27], MD; Albrecht Günther[27], MD; Gerhard F. Hamann[28], MD; Hannes Lücking[29], MD; Arnd Dörfler[29], MD; Muhammad Fawad Ishfaq[30], MD; Jason J Chang[31], MD; Fernando D. Testai[32], MD; Daniel Woo[33], MD; Andrei V. Alexandrov[30], MD; Dimitre Staykov[1], MD; Nitin Goyal[30], MD; Georgios Tsivgoulis[30,34], MD; Kevin N Sheth[5], MD; Issam A. Awad[35], MD; Stefan Schwab[1,+], MD; Daniel F. Hanley[2,+], MD; and Hagen B. Huttner [1,*,+], MD.

[1]Department of Neurology, University of Erlangen-Nuremberg, Germany; [2]Division of Brain Injury Outcomes, Johns Hopkins University, USA; [3]Department of Neurology, University of Freiburg; [4]Department of Neurology, Yale University School of Medicine, USA; [5]Department of Neurosurgery, Yale University School of Medicine, USA; [6]Beth Israel Deaconess Medical Center, Harvard Medical School, USA; [7]Department of Neurology, Charité–Universitätsmedizin Berlin, Germany; [8]Center for Stroke Research Berlin, Germany; [9]German Centre for Cardiovascular Research(DZHK), Germany; [10]German Center for Neurodegenerative Diseases(DZNE), Germany; [11]Department of Neurosurgery, Charité–Universitätsmedizin Berlin, Germany; [12]Department of Neurology, Heidelberg University Hospital, Germany; [13]Department of Neurology, University of Würzburg, Germany; [14]Department of Neurology, University of Ulm, Germany; [15]Department of Neurology, Nuremberg General Hospital, Germany; [16]Department of Neurology and Neurogeriatry, Johannes Wesling Medical Center Minden, Germany; [17]Department of Neurosurgery, Johannes Wesling Medical Center Minden, Germany; [18]Department of Neurology, University of Cologne, Germany; [19]Department of Neurology, LVR-

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Hospital Bonn, Germany; [20]Department of Neurology, University of Münster, Germany; [21]Department of Neurology, University of Dresden, Germany; [22]Department of Neurology, Klinikum Augsburg, Germany; [23]Department of Neurology, Asklepios Klinikum Hamburg Altona, Germany; [24]Department of Neurology, Klinikum Dortmund, Germany; [25]Department of Neurology, Klinikum Stuttgart, Germany; [26]Department of Neurology, University of Leipzig, Germany; [27]Department of Neurology, University of Jena, Germany; [28]Department of Neurology and Neurological Rehabilitation, Bezirkskrankenhaus Günzburg, Germany; [29]Department of Neuroradiology, University of Erlangen-Nuremberg, Germany; [30]Department of Neurology, University of Tennessee Health Science Center, USA; [31]Department of Critical Care Medicine, MedStar Washington Hospital Center, USA; [32]Department of Neurology and Rehabilitation, University of Illinois College of Medicine, USA; [33]Department of Neurology and Rehabilitation Medicine, University of Cincinnati, USA; [34]Second Department of Neurology, Attikon University Hospital, School of Medicine, Greece. [35]Department of Neurosurgery, University of Chicago, USA. [36]Department of Neurology, Helios Klinikum Berlin-Buch, Germany; [37]Department of Neurology, Klinikum Koblenz, Germany; [38]Department of Neurology, Klinikum Bad Hersfeld, Germany; [39]Department of Neurology, Klinikum der Stadt Ludwigshafen am Rhein, Germany;

[+] These authors contributed equally; [&]deceased during study period;

[*]Corresponding author: Hagen B. Huttner, Department of Neurology, University of Erlangen-Nuremberg, Germany

Corresponding author's address: Schwabachanlage 6, 91054 Erlangen, Germany

Corresponding author's phone and fax: phone:+4991318544523;fax:+4991318536597

Corresponding author's e-mail address: Hagen.Huttner@uk-erlangen.de

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Abstract

Background: In patients with intracerebral hemorrhage (ICH) the presence of intraventricular hemorrhage (IVH) constitutes a promising therapeutic target. Intraventricular fibrinolysis (IVF) reduces mortality, yet impact on functional disability remains unclear. Thus, we aimed to determine the influence of IVF on functional outcomes.

Methods: This individual participant data (IPD) meta-analysis pooled 1,501 patients from two randomized trials and seven observational studies enrolled during 2004 to 2015. We compared IVF vs standard of care (SoC, including placebo) in patients treated with external ventricular drainage due to acute hydrocephalus caused by ICH and/or IVH. The primary outcome was functional disability evaluated by the modified Rankin Scale (mRS, range:0-6, lower scores indicating less disability) at 6 months, dichotomized into mRS:0-3 vs mRS:4-6. Secondary outcomes included ordinal-shift analysis, all-cause mortality, and intracranial adverse events. Confounding and bias were adjusted by random-effects- and doubly-robust-models to calculate odds-ratios (OR) and absolute treatment-effects (ATE).

Results: Comparing treatment of 596 with IVF to 905 with SoC resulted in an ATE to achieve the primary outcome of 9.3%[95%CI4.4-14.1]. IVF treatment showed a significant shift towards improved outcome across the entire range of mRS estimates, common-OR:1.75[95%CI 1.39-2.17], reduced mortality, OR:0.47[95%CI 0.35-0.64], without increased adverse events, absolute difference:1.0%[95%CI -2.7-4.8]. Exploratory analyses provided that early IVF-treatment (≤48 hours) after symptom onset was associated with an ATE:15.2%[95%CI 8.6-21.8] to achieve the primary outcome.

Conclusions: As compared to SoC, the administration of IVF in patients with acute hydrocephalus caused by 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.

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Non-standard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
IVF	intraventricular fibrinolysis
IPD	individual participant data
SoC	standard of care
mRS	modified Rankin Scale
OR	odds-ratio
ATE	absolute treatment-effects
EVD	external ventricular drainage
GCS	Glasgow Coma Scale
GLM	generalized linear mixed-effect
AIPW	augmented inverse probability weighting
CLEAR III	Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III
ERICH	Ethnic/Racial Variations of Intracerebral Hemorrhage study
RETRACE	German-wide multicenter analysis of oral anticoagulation associated intracerebral hemorrhage study
UKER	observational cohort study spontaneous ICH conducted at the University Hospital Erlangen
UTHSC	University of Tennessee Health Science Center
BIDMC	Beth Israel Deaconess Medical Center
AD	absolute difference
SMD	standardized mean difference
RCT	randomized controlled trial

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INTRODUCTION

Intraventricular fibrinolysis(IVF) is a treatment strategy in patients with intracerebral hemorrhage(ICH) and severe ventricular involvement(IVH)[1,2]. Several studies demonstrated hastened intraventricular clot resolution by IVF and the randomized controlled CLEAR-III trial verified prior demonstration of safety(bleeding complications and infections) compared to placebo treatment in an ICH population with smaller parenchymal but larger intraventricular hemorrhage volumes[3,4]. Mortality rates were reduced, but the primary efficacy analysis for functional outcome was neutral[3,5]. Questions remain whether improved patient selection may provide functional benefit and establish this therapy with greater certainty[3,6,7].

Two important sub-groups have been identified from CLEAR-III, patients with intermediate sized IVH volumes and time from symptom onset to randomization[3]. Hence, individualizing a treatment strategy suggests that threshold-based selection of lesion volumes and timing from symptom onset to IVF treatment may provide functional benefit. Only availability of a large sample with highly granular data would allow quantification of patient characteristics predictive of favorable functional outcome[8-10]. We thus conducted an individual participant data(IPD) meta-analysis integrating published studies on IVF and eligible ICH patients from large observational cohort studies[11].

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and after approval of the data coordinating centers of the participating trials and studies.

Search Strategy and Data Synthesis

We performed a systematic review searching the Cochrane Library, Pubmed and Scopus databases, and international trial registries, without language restrictions for clinical studies from inception to July30, 2019. Full details of search criteria for the systematic review, aggregate data meta-analysis, and statistical analysis plan, please see supplemental material(**Methods,TableS1,FigureS1-3**). The systematic review identified 8 studies of which 3 fulfilled pre-specified criteria for IPD contribution and after invitation two contributed IPD[3,12,13]. Hence, decision was made by the lead investigators (JBK,WZ,STG,SS,DFH,HBH) to complement the

present analysis by integrating further IPD from existing large studies of general ICH-populations with availability of highly granular data[3,12,14-19]. This decision was based on the fact that with these few available specific studies analytical methodology would have been limited by restricting appropriate adjustments for bias and confounding as well as leading to an inability to conduct sufficient exploratory analyses(**Supplemental Methods).** Identification of observational studies was performed by screening registries(ClinicalTrials.gov,European Clinical Trials Database), complemented by our systematic review, and by contacting established investigative teams. All findings are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data(PRISMA-IPD)[20].

The present IPD meta-analysis(**FigureS1**) incorporated 9 studies(supplemental material,**TableS2**): 1) the randomized controlled CLEAR-III trial(NCT00784134), 2) CLEAR-B phase-II trial(NCT00650858)[3,4], 3) the multi-center, prospective, case-control Ethnic/Racial Variations of Intracerebral Hemorrhage(ERICH) study(NCT01202864)[15], 4&5) two multi-center cohorts from the German-wide multicenter analysis of oral anticoagulation associated intracerebral hemorrhage, RETRACE-study part-I(NCT01829581)[14] and part-II(NCT03093233)[16,21], 6) the single-center observational cohort study(UKER) for primary spontaneous ICH conducted at the University Hospital Erlangen, Germany(NCT03183167)[17], 7) single-center observational cohort study in adult nontraumatic ICH patients conducted at the University of Tennessee Health Science Center, USA[18], 8) single-center observational cohort study in adult patients with spontaneous supratentorial ICH conducted at Beth Israel Deaconess Medical Center, USA[19], 9) single-center matched-pair cohort study conducted at University Hospital Heidelberg, Germany[12]. Informed consent was obtained from all participants or their legal representatives within each participating study if not waived by the respective ethical committees. Institutional review boards or ethical committees reviewed and approved all study protocols.

Data Extraction and Study Population

Eligibility for IPD inclusion comprised the following: 1) supratentorial primary ICH or IVH with IVH causing acute hydrocephalus treated with an external ventricular drainage(EVD), 2) patient age≥18years, 3) pre-morbid modified Rankin Scale(mRS)≤3, 4) >10 patients treated with IVF within each study framework, 5) no evidence of early care limitations or death within 48 hours after admission[22], 6) no evidence of secondary ICH-etiologies,

7) no other competing treatment intervention(e.g. craniectomy,minimal invasive surgery), 8) use of validated methods for imaging assessment, 9) standardized scoring of neurological status(Glasgow Coma Scale,GCS, ranging from 3, comatose, to 15, alert), and 10) availability of standardized functional outcome assessed by the mRS(ranging from 0, no functional deficit to 6, death) recorded between 3-12 months after the index event. For methodology of data acquisition and description of included studies, please see supplement(**TableS3**). Complete data sets were available for patient identification; i.e. the entire ICH cohort within each study framework was available for identification of patients eligible for IPD contribution according to the pre-defined eligibility criteria. Baseline data on demographics, prior comorbidities, prior medication exposures, timing measures, and neurological status upon hospital admission were obtained[16]. Imaging analyses were conducted at imaging-cores within each study frame-work by investigators blinded to clinical information(**TableS3**). The IPD-set was compiled and centrally analyzed by the coordinating center(University Hospital Erlangen,Germany)[16].

Intervention and Outcomes

The investigated intervention(intraventricular fibrinolysis,IVF) consisted of the instillation of alteplase(1mg/ml) through an EVD until the stopping point was achieved. The stopping point was defined as radiographic opening of the 3rd and 4th ventricles, and/or relieved mass effect of IVH, or reached maximum dose according to individual study protocols[3,4,12]. IVF was compared to either placebo treatment(CLEAR-III) or EVD-management according to American or European ICH-guidelines, both referred to as standard of care(SoC) throughout the manuscript[23,24].

The primary outcome was pre-defined as the proportion of patients achieving favorable functional outcome at 6 months mRS:0-3 dichotomously compared to mRS:4-6. Secondary outcomes comprised 1) ordinal shift analysis of mRS values at 6 months, 2) all-cause mortality at 6 months, and 3) adverse events defined as any intracranial bleeding complication or bacterial infection occurring within 30 days after ictus. Follow-up information was obtained according to individual study protocols by personnel blinded to clinical data(**TableS3**).

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Risk of Bias Assessment

All included studies were evaluated for risk of bias using the ROBINS-I tool(Risk Of Bias In Non-randomized Studies of Interventions)[25] by consensus of the lead authors(**TableS4**).

Statistical Analysis

Full details of the prespecified statistical analysis plan of this IPD meta-analysis are provided in the supplemental material (**Supplemental Methods**). Each IPD-set was checked for completeness, consistency and queries were resolved with participating investigators. We standardized coding, format, and units of measurement for scale or continuous variables to maximize data-completeness[26]. Missing outcome information(5.4%, complete IPD-dataset) was handled by multiple imputations(**Supplemental Methods, TableS4**)[27]. Sensitivity analyses involved inter-study variance of treatment effects across participating studies with clinical outcomes at 6 months, confounding due to excluded patients determined by interaction analysis(IVF*excluded patients), and evaluation of unmeasured confounding(e-values)[9,28]. Heterogeneity was evaluated by Cochran-Q testing, calculated I^2-values, considered significant p-values<0.1, and inconsistency of results were determined according to the GRADE-Handbook[29]. Analyses for interactions of treatment effect(IVF*interaction term) were considered significant for p-values<0.05. All tests were 2-sided with significance level at α=0.05. The systematic review and aggregate meta-analysis were conducted using RevMan(Version5.4) and IPD meta-analysis was conducted with STATA(Version14.2).

Statistical analyses of primary and secondary outcomes used pooled IPD(n=1,501) comparing IVF treatment, as per-protocol basis, to SoC as reference. To rigorously address bias and confounding, we used three different confounder-adjusted methods conducted as one-stage approach to calculate adjusted odds ratios(OR) and adjusted absolute treatment effects(ATE). 1) Conventional OR-model calculated using generalized linear mixed-effect(GLM) to analyze all studies simultaneously, accounting for clustering of treatment effects(between-study differences) across participating studies with random effects and adjustments for confounders associated with the investigated outcomes. 2) Doubly robust estimations to calculate ATE using logistic regression by a technique(augmented inverse probability weighting,AIPW) which was identified as most conservative model after sensitivity analyses. Adjustments were performed in two ways; A) confounders associated with an

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increased propensity to receive IVF treatment, i.e. oral anticoagulation, GCS, deep ICH-location, ICH-volume, IVH-volume, and B) validated confounders associated with functional outcome and mortality, i.e. age, pre-stroke mRS, oral anticoagulation, GCS, thalamic ICH-location, ICH-volume, IVH-volume. 3) For graphical analyses only, we used a propensity-matched cohort(n=1,150) using the aforementioned confounders associated with an increased treatment propensity, calculated by balanced, parallel(1:1) nearest neighbor approach(caliper:0.2).[30] Analyses comprised the mRS distribution at 6 months and exploratory threshold regression analyses of non-linear treatment effect modifiers(age, GCS, ICH- & IVH-volume, symptom onset to treatment) calculated using the multivariable fractional polynomials interaction approach with OR presented on a log-odds scale[31].

In general, confounders were identified based on sensitivity analyses of each investigated outcome and considered relevant by a standardized mean difference larger than 10%. Primary and secondary outcome analyses comprised binary regression for the primary endpoint(mRS 0-3), mortality, and adverse events as well as ordinal shift analyses(presented as common odds ratio, after checking the proportional odds assumption, as appropriate) across the entire mRS within GLM- and AIPW-modelling. Exploratory subgroup analyses followed the same methodology. Subgroup categories of continuous or scale variables were grouped into tertiles or scored as present or absent, and were tested for interactions(IVF*sub-group category) considered significant for p-values<0.05.

RESULTS

Systematic Review and Aggregate Data Meta-analysis

The systematic review of published studies analyzing associations of IVF with mortality at discharge, mortality and functional outcome at ≥3 months identified two trials and 6 observational cohort studies(**TableS1,FigureS1**). Results provided significant heterogeneity and substantial data inconsistency for functional outcome(**FigureS2**). Risk of bias due to baseline confounding was judged high or unclear in 6 out of 8 studies(**FigureS3**).

Study Population of Individual Participant Data Meta-Analysis

We screened 9 datasets with 8,482 ICH-patients for eligibility, pooling IPD data from one randomized controlled trial (CLEAR-III, including N=500), from one phase-II trial(CLEAR-B, including N=35), from one observational study (including N=52), and additionally integrated IPD from large observational cohort studies(ERICH, including N=388; RETRACE-I, including N=115; RETRACE-II, including N=144; UKER, including N=170; UTSHC, including N=80; BIDMC, including N=17). Hence, the IPD study cohort consisted of 1,501 patients of which 596 patients received IVF compared to 905 patients with SoC(**Figure1**). Sensitivity analyses of excluded patients did not show significant interactions(**TableS5**).

Risk of Bias Assessment

Statistical heterogeneity was not significant and inconsistency of results across participating studies with respect to inter-study variance of treatment associations was determined low(I^2-fluctuation span, 0%-47%; **FigureS4**). Risk of bias was judged low to moderate risk across all participating studies(**FigureS4**,**TableS4**).

IPD-Meta-Analysis

Baseline characteristics are provided in **Table1**. Patients with IVF received the first dose at a median of 47.8hours IQR(31.0-64.5) after symptom onset with a median cumulative dose of 5mg alteplase IQR(3-8) and 95%CI(0-12). We identified significant imbalances in IVF treated patients compared to SoC, i.e. less frequent prior use of oral anticoagulation(absolute difference[AD]-6.5%,95%CI(-10.7--2.2), standardized mean difference[SMD]-0.16), more frequent deep ICH-location(AD:4.1%,95%CI(-0.1-8.2),SMD:0.10), less frequent higher GCS(values=13-15,AD:6.0%,95%CI(-10.6--1.4),SMD:-0.11), smaller ICH-volumes(AD:-6.0ml,95%CI(-7.9--4.1),SMD:-0.54), and larger IVH volumes(AD:6.0ml,95%CI(3.3-8.7),SMD:0.30). Sensitivity analyses dichotomized according to functional outcome(mRS:0-3 at 6 months,**TableS6**) showed more frequent IVF-use(AD:12.2%,95%CI(6.8-17.4),SMD:0.25), younger age(AD:-7.5yrs,95%CI(-8.8--6.2),SMD:-0.62), higher GCS values(AD:3.0,95%CI(2.3-3.7),SMD:0.57), less frequent thalamic ICH(AD:-9.7%,95%CI(-15.3--4.1),SMD:-0.19), lower ICH-volumes(AD:-9.7ml,95%CI(-11.5--8.0),SMD:-0.59), and lower IVH-volumes(AD:-8.0ml,95%CI(-10.9--5.1),SMD:-0.45) in patients with favorable outcome. Sensitivity analyses according to adverse events showed more frequent prior oral anticoagulant use(AD:9.2%,95%CI(2.5-15.8),SMD:0.21) and larger IVH-volumes(AD:3.8ml,95%CI(0.2-7.4),SMD:0.10;**TableS7**).