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ORIGINAL ARTICLE

The KEEP SIMPLEST Study: Improving In-House Delays and Periinterventional Management in Stroke Thrombectomy—A Matched Pair Analysis

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Abstract

Background and Purpose: Although the treatment window for mechanical thrombectomy (MT) in patients with acute ischemic stroke (AIS) has been extended in recent years, it has been proven that recanalizing treatment must be administered as soon as possible. We present a new standard operating procedure (SOP) to reduce in-house delay, standardize periinterventional management and improve patient safety during MT.

Methods: KEep Evaluating Protocol Simplification In Managing Periinterventional Light Sedation for Endovascular Stroke Treatment (KEEP SIMPLEST) was a prospective, single-center observational study aimed to compare aspects of periinterventional management in AIS patients treated according to our new SOP using a combination of esketamine and propofol with patients having been randomized into conscious sedation (CS) in the Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) trial. Primary outcome was early neurological improvement at 24h using the National Institutes of Health Stroke Scale, and secondary outcomes were door-to-recanalization, recanalization grade, conversion rate and modified Rankin Scale (mRS) at 3 months.

Results: Door-to-recanalization time (128.6 ± 69.47 min vs. 156.8 ± 75.91 min; $p = 0.02$), mean duration of MT (92.01 ± 52 min vs. 131.9 ± 64.03 min; $p < 0.001$), door-to-first angiographic image (51.61 ± 31.7 min vs. 64.23 ± 21.53 min; $p = 0.003$) and computed tomography-to-first angiographic image time (31.61 ± 20.6 min vs. 44.61 ± 19.3 min; $p < 0.001$) were significantly shorter in the group treated under the new SOP. There were no differences in early neurological improvement, mRS at 3 months or other secondary outcomes between the groups. Conversion rates of CS to general anesthesia were similar in both groups.

Conclusion: An SOP using a novel sedation regimen and optimization of equipment and procedures directed at a leaner, more integrative and compact periinterventional management can reduce in-house treatment delays significantly in stroke patients receiving thrombectomy in light sedation and demonstrated the safety and feasibility of our improved approach.

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Introduction

Large randomized clinical trials have demonstrated the benefit of mechanical thrombectomy (MT) in an extended time of up to 6 h in patients with proximal vessel occlusion and acute ischemic stroke (AIS) of the anterior circulation [1]. Selected patients may even benefit an extended time window of up to 16 or 24 h [2–4]. However, time-to-recanalization remains the probably most critical factor in achieving better clinical outcomes for stroke patients [5].

Triage systems in the emergency room (ER) are used to identify patients with a high probability of large-vessel stroke [6]. Some centers have advocated skipping the ER altogether by taking potential stroke patients directly to the computed tomography (CT) scanner or the angiography suite upon presentation [7, 8]. Early activation of the team responsible for periinterventional management of MT patients and the use of established standard operating procedures (SOP) are other potentially important ways to increase the efficiency of acute stroke treatment [9–11].

We have been developing the Heidelberg in-house SOP for periinterventional management since 2009 to optimize the in-house workflow and reduce the door-to-groin times to enhance patient's chance of improved clinical outcome without loss of safety. This SOP was used in our Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) trial, the first published randomized clinical trial on periinterventional management comparing conscious sedation (CS) with general anesthesia (GA). SIESTA showed no statistically significant difference with regard to the primary outcome of early neurological improvement [12]. These results were corroborated by two other recently published prospective trials [13, 14]. At the Heidelberg stroke center, the SOP for CS included a combination of propofol and remifentanil as an alternative sedation regimen in MT and led to a new SOP being developed involving streamlined protocols for periinterventional processes and a more compact and integrative setup of technical equipment to save time, maximize efficiency and at the same time enhance safety. We also introduced and established a new sedation regimen using the combination of esketamine and propofol. This prospective study was conducted to compare our new SOP for MT with the periinterventional management of patients in the CS group of the SIESTA trial.

Methods

Design of the KEEP SIMPLEST Study

KEep Evaluating Protocol Simplification In Managing Periinterventional Light sedation for Endovascular Stroke Treatment (KEEP SIMPLEST) was a prospective, single-center observational study designed to compare periinterventional management of AIS patients according to our new SOP with that of patients randomized into the CS group of the SIESTA trial [12]. The experimental study population for KEEP SIMPLEST was selected to be comparable to the patients of the CS group of the SIESTA trial using propensity score matching. The primary outcome was early neurological improvement defined by change in National Institutes of Health Stroke Scale (NIHSS) score between admission and after 24 h as in SIESTA. The prespecified secondary outcomes included functional outcome at 3 months assessed by the modified Rankin Scale (mRS). Other secondary outcomes included in-hospital and 3-month mortality, periinterventional safety (assessed by critical hypertension (systolic blood pressure > 180 mmHg) or hypotension (systolic blood pressure < 120 mmHg), ventilation or oxygenation disturbance, and procedural complications), or time window of recanalization (e.g., door-to-recanalization or groin puncture-to-recanalization times) congruent to the prespecified outcomes of the SIESTA trial [15]. The trial was approved by our institutional review board (Ethikkommission Medizinische Fakultät Heidelberg, ID S-325/2015).

Modified SOP Endovascular Stroke Treatment

Periinterventional management in both groups was conducted entirely by our team made up of one nurse specialized in neurocritical care and one neurointensivist from our neurocritical care unit (NICU) trained in the

(See figure on next page.)

Fig. 1 Standard operating procedure endovascular stroke treatment used in KEEP SIMPLEST. *GCS* Glasgow Coma Scale, *EST* endovascular stroke treatment, *CS* conscious sedation, *GA* general anesthesia, *ICA* internal carotid artery, *MCA* middle cerebral artery, *VA* vertebral artery, *BA* basilar artery, *ER* emergency room, *NICU* neurointensive care unit, *M-ICU* mobile ICU, *BP* blood pressure, *ECG* electrocardiography, SpO_2 peripheral capillary oxygen saturation, $etCO_2$ end-tidal carbon dioxide, *RASS* Richmond Agitation Sedation Scale, *CCT* cerebral computed tomography, *MRI* magnetic resonance tomography, *ASPECTS* Alberta stroke program early CT score, *HR* heart rate, *LA* local anesthesia, *MRA* magnetic resonance angiography, *tPA* tissue plasminogen activator, *ICH* intracerebral hemorrhage

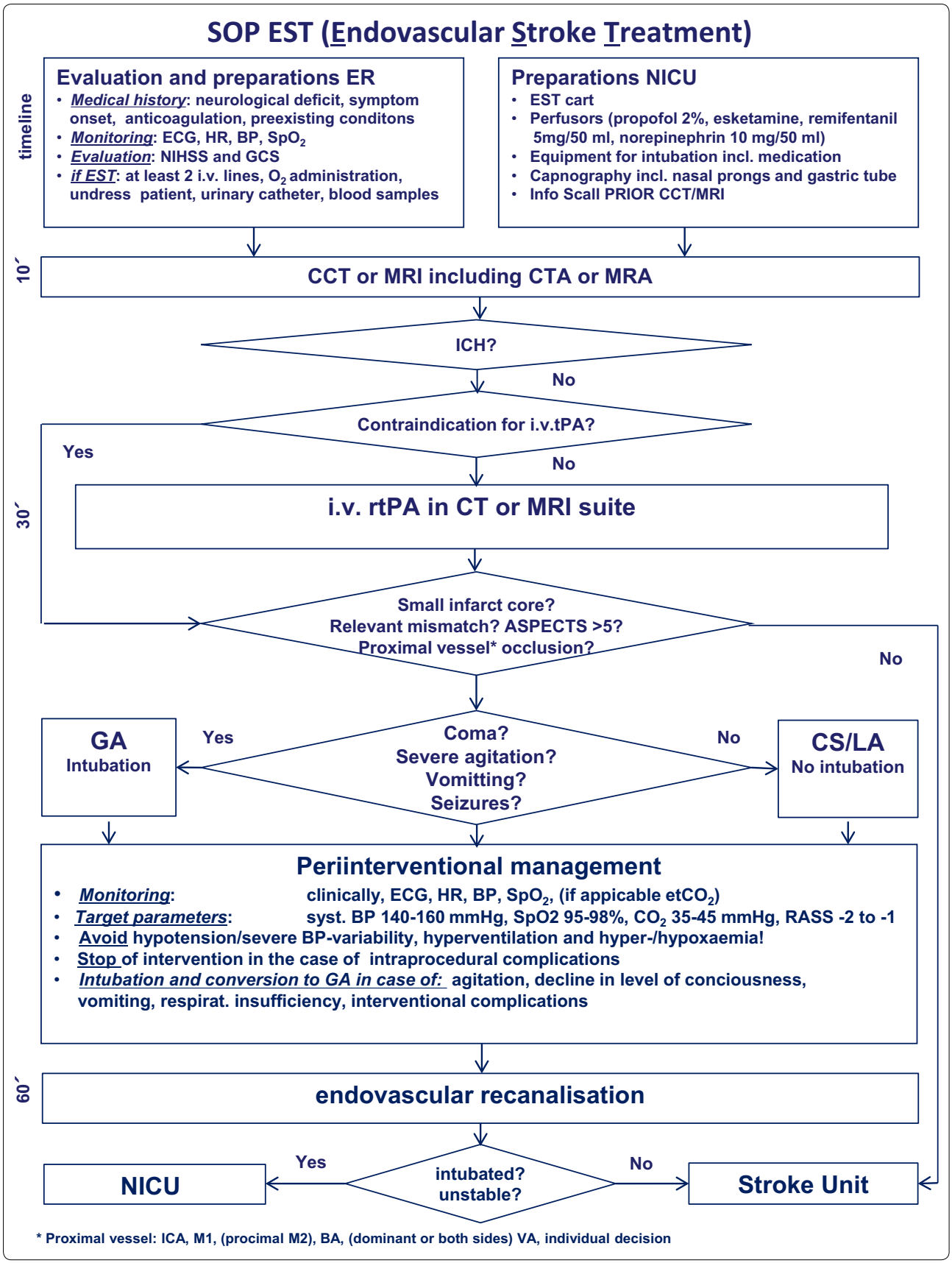
SOP EST (Endovascular Stroke Treatment)
timeline
Evaluation and preparations ER
• Medical history: neurological deficit, symptom onset, anticoagulation, preexisting conditons
• Monitoring: ECG, HR, BP, SpO2
• Evaluation: NIHSS and GCS
• if EST: at least 2 i.v. lines, O2 administration, undress patient, urinary catheter, blood samples
Preparations NICU
• EST cart
• Perfusors (propofol 2%, esketamine, remifentanil 5mg/50 ml, norepinephrin 10 mg/50 ml)
• Equipment for intubation incl. medication
• Capnography incl. nasal prongs and gastric tube
• Info Scall PRIOR CCT/MRI
10´
CCT or MRI including CTA or MRA
ICH?
No
Contraindication for i.v.tPA?
Yes
No
30´
i.v. rtPA in CT or MRI suite
Small infarct core?
Relevant mismatch? ASPECTS >5?
Proximal vessel* occlusion?
No
GA
Intubation
Yes
Coma?
Severe agitation?
Vomitting?
Seizures?
No
CS/LA
No intubation
Periinterventional management
• Monitoring: clinically, ECG, HR, BP, SpO2, (if appicable etCO2)
• Target parameters: syst. BP 140-160 mmHg, SpO2 95-98%, CO2 35-45 mmHg, RASS -2 to -1
• Avoid hypotension/severe BP-variability, hyperventilation and hyper-/hypoxaemia!
• Stop of intervention in the case of intraprocedural complications
• Intubation and conversion to GA in case of: agitation, decline in level of conciousness, vomiting, respirat. insufficiency, interventional complications
60´
endovascular recanalisation
Yes
intubated?
unstable?
No
NICU
Stroke Unit
* Proximal vessel: ICA, M1, (procimal M2), BA, (dominant or both sides) VA, individual decision

Table 1 Main differences between the two SOPs

Differences	SIESTA	KEEP SIMPLEST
Gastric tube	×	–
Neuromonitoring (BIS, NIRS)	×	–
Pre-prepared catecholamines	–	×
Pre-prepared intubation equipment	×	×
Scall* information prior CT/MRI	–	×
EST cart (including mechanical ventilator, suction, capnography, infusion pumps, monitoring)	–	×
Favored post-MT treatment on stroke unit	–	×
Propofol	×	×
Esketamine	×	×
Routinely remifentanil	×	–

BIS bispectral index, *CT* computed tomography, *EST* endovascular stroke treatment, *KEEP SIMPLEST* KEep Evaluating Protocol Simplification In Managing Periinterventional Light Sedation for Endovascular Stroke Treatment, *MRI* magnetic resonance imaging, *MT* mechanical thrombectomy, *NIRS* near-infrared spectroscopy, *SIESTA* Sedation versus Intubation for Endovascular Stroke TreAtment, *SOP* standard operating procedures

*Scall is defined as the neurointensivist on call for the periinterventional management of acute stroke treatment

interventional setting. The new in-house SOP (Fig. 1) is based on the SOPs for CS and GA, respectively, used in the SIESTA trial. However, we have made several adjustments in conducting MT in CS (Table 1). The main innovation has been the implementation of our new mobile endovascular stroke treatment (EST) cart (Online supplement Figure 1) consisting of one cart outfitted with the complete equipment necessary for conducting periinterventional management for MT. The equipping of the cart (e.g., with medication that otherwise deteriorates over a short time) is completed by one nurse and one neurointensivist as soon as the decision is made to conduct an MT. The advantage of the EST cart is that it combines all necessary equipment in one mobile unit and is ready to be used at any time, thus reducing preparation times considerably. The cart can be attached to a regular patient bed and contains the following equipment elements: basis monitoring (including electrocardiogram, heart rate, peripheral blood pressure, oxygen saturation), infusion pumps, mobile suction, respirator (including capnography), capnography for spontaneously breathing patients. Other alterations were that we discontinued the placement of a gastric tube before EST and the installation of enhanced neuromonitoring (bispectral index, near-infrared spectroscopy). Furthermore, we introduced protocol parts in which the NICU team is informed before imaging is performed, hence before a final decision has been made. Infusion pumps with norepinephrine (0.2 mg/ml), 0.9% sodium chloride solution and an infusion with crystalline fluids (Sterofundin™) were prepared once daily or after each intervention to save time. Only the sedatives (propofol (20 mg/ml), esketamine (25 mg/ml) and remifentanil (0.1 mg/ml) were drawn up after the decision for an intervention was made. Hypotension was avoided by administration of norepinephrine or crystalline fluids. All patients in the SIESTA and KEEP SIMPLEST trial were treated according to identical strict blood pressure targets (systolic blood pressure 140–160 mmHg) defined in the respective SOPs. Finally, we changed the combination of sedatives used in our new SOP to propofol and esketamine (vs. propofol and remifentanil used previously) in an attempt to reduce the use of opioids and catecholamines. If the patient met the criteria for CS, anesthesia was initiated using short-acting sedatives (mostly a combination of propofol and esketamine) and remifentanil if analgesia was deemed necessary. All patients also received local anesthesia at the site of the groin puncture. Patients who showed signs of respiratory failure, lost their protective reflexes or experienced refractory agitation were intubated in the angiography suite. Monitoring of vital signs (electrocardiogram, heart rate and blood pressure) was performed continuously and at regular intervals (noninvasive blood pressure every 5 min) throughout the procedure. Patients were transferred directly to our stroke unit after the intervention was completed, and only patients that required mechanical ventilation or patients with cardiorespiratory instability were transferred to our NICU.

Statistical Analysis

The matching procedure was done by a propensity score approach [16]. The propensity score was estimated by a logistic regression model using group as outcome variable. Age, NIHSS on admission, premorbid mRS and the Alberta stroke program early CT score (ASPECTS) were included as matching variables. Based on those scores, a 1:1 matching was performed. The matching was done on the logit of the propensity score using a caliper of 0.2 of the standard deviation of the logit of the propensity score [16]. The CS group (SIESTA) consisted of 77 patients, 74 of which were considered in the matching procedure (complete data in matching variables and target variable). After 51 patients were included in the KEEP SIMPLEST study arm, an interim analysis was performed to estimate the matching rate and to calculate the number of patients needed to expect a matching partner to all patients of the SIESTA data set. At interim analysis, 51 patients of the SIESTA data were randomly chosen to estimate the matching rate. We projected the required sample size by employing the lower limit of the 95% confidence interval for the matching rate. The primary outcome (difference in NIHSS between admission and after 24h) was analyzed

using a linear mixed effects model which includes fixed and random effects. We considered group and NIHSS on admission as fixed effects, the matched pairs were included as random effects. The estimated mean difference between the groups (fixed effect in the mixed model) together with 95% confidence intervals and *p* values is presented. The evaluation of secondary outcomes was done using the paired *t* test for continuous variables, the Wilcoxon signed-rank test for ordinally scaled variables, the McNemar test for categorical variables and the Bowker test for categorical variables with more than two categories. All *p* values are of descriptive nature.

In a subgroup analysis assessing variables measuring time interval, we excluded patients who were transferred from other hospitals directly to the angiography suite to avoid bias. It is important to note that the groups considered for sensitivity analyses may differ with regard to baseline characteristics, because it may occur that not both patients of a matched pair are included in the considered subgroup. For analyzing secondary endpoints in subgroups, we performed the unpaired *t* test.

Results

Patient Characteristics

The control (CS) group of SIESTA consisted of 77 patients from which 74 were considered in the matching analysis. Of the 161 patients enrolled in KEEP SIMPLEST, 154 had a complete data set. The matching rate at interim analysis (51 patients in the KEEP SIMPLEST and the control group) was 0.544, and the lower limit of the 95% confidence interval was 0.461, which resulted in a total sample size of 161 (=74/0.661). The final KEEP SIMPLEST data set consists of 154 patients with complete data (161 patients were included in the trial, but 7 patients had a missing ASPECTS score). The matching procedure reached a matching rate of 0.932, and hence 69 pairs were found and analyzed as experimental group. Thus, a total of 138 patients were considered for the analysis of the primary and secondary outcomes.

The baseline, demographic and clinical characteristics of the matched patients are shown in Table 2. In the study population, mean age was 72 years, baseline median NIHSS was 17, and 62.3% of the control group and 49.3% of the experimental group received IV thrombolysis with recombinant tissue-type plasminogen activator (tPA). Complete reperfusion (thrombolysis in cerebral infarction (TICI) 2b, 2c or 3) was achieved in 79.7% versus 88.4%, improvement in 24h-NIHSS was almost identical (-4.3 ± 7.7 vs. -3.8 ± 10.5), and mRS 0–2 at 3 months was 20.2% versus. 31.3% between control and experimental groups.

Table 2 Baseline characteristics and demographics

Characteristic	SIESTA (*N* = 69)	KEEP SIMPLEST (*N* = 69)	*p* values
Demographic characteristics			
Age (yr)			
Mean (SD)	72 (14.7)	72.7 (12.4)	0.79
Female sex—no. (%)	32 (46.4)	36 (52.2)	0.64
Premedication—no. (%)			
Antiplatelets			0.85
No	45 (68.2)	44 (63.8)	
Oral anticoagulants			0.06
No	51 (75.0)	60 (87)	
Statin			1.0
No	48 (71.6)	51 (73.9)	
Vascular risk factors—no. (%)			
Hypertension	49 (71.0)	55 (79.7)	0.29
Diabetes mellitus	17 (24.6)	14 (20.3)	0.7
Hyperlipidemia	22 (31.9)	12 (17.4)	0.09
Smoking	12 (17.6)	12 (17.4)	1.0
Heart failure	19 (27.5)	13 (18.8)	0.26
Atrial fibrillation	34 (49.3)	20 (29)	0.12
Peripheral artery occlusive disease	5 (7.5)	4 (5.8)	1.0
Pretreatment imaging—no. (%)			
Imaging			
CT	56 (81.2)	63 (91.3)	0.12
ASPECTS*—no. (%)			0.73
10–8	42 (60.8)	39 (56.5)	
7–6	21 (30.4)	21 (30.4)	
< 6	6 (8.6)	9 (13)	
Median (IQR)	8 (7–9)	8 (6.25–9)	
Scores on admission—no. (%)			
Premorbid mRS			0.84
0	32 (46.4)	32 (46.4)	
1	18 (26.1)	17 (24.6)	
2	13 (18.8)	15 (21.7)	
> 2	6 (8.7)	5 (7.2)	
NIHSS on admission			0.72
Mean (SD)	17.2 (3.7)	16.9 (6.8)	
Occlusion—no. (%)			0.005
Occlusion			
MCA	45 (65.1)	43 (62.3)	
ICA	8 (11.2)	0	
ICA + MCA	16 (23.1)	25 (36.2)	
Occlusion side left	37 (54.9)	38 (49.8)	0.59
Treatment of stroke			0.12
No intervention	0 (0.0)	2 (2.9)	
Lysis + EST	43 (62.3)	34 (49.3)	
EST	25 (36.2)	23 (33.3)	
Stenting	1 (1.4)	10 (14.5)	

ASPECTS Alberta Stroke Program Early CT Score, *CT* computed tomography, *CS* conscious sedation, *EST* endovascular stroke treatment, *GA* general anesthesia, *GCS* Glasgow Coma Scale, *ICA* internal carotid artery, *IQR* interquartile

Table 2 (continued)

range, *KEEP SIMPLEST* KEep Evaluating Protocol Simplification In Managing Periinterventional Light Sedation for Endovascular Stroke Treatment, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *mRS* modified Rankin Scale, *N/no.* number, *NIHSS* National Institutes of Health Stroke Scale, *SD* standard deviation, *SIESTA* Sedation versus Intubation for Endovascular Stroke TreAtment, *Yr* years

Propensity Score-Adjusted Outcomes

Propensity score-adjusted primary and secondary outcomes are shown in Table 3. Following 1:1 matching, thrombectomy patients who received CS according to our new SOP within the KEEP SIMPLEST study had significantly lower mean door-to-recanalization times (128.6 ± 69.5 min vs. 156.8 ± 75.9 min; $p = 0.025$) as well as mean duration of EST times (92.01 ± 52.0 min vs. 131.9 ± 64.0 min; $p < 0.001$). Likewise, the mean door-to-first angiographic image time (51.6 ± 31.7 min vs. 64.2 ± 21.5 min; $p = 0.003$) and the mean CT-to-first angiographic image time were significantly shorter in the experimental group (31.6 ± 20.6 min vs. 44.6 ± 19.3 min; $p < 0.001$). We did not find significant differences between the two groups in the primary outcome improvement of NIHSS after 24 h and in the secondary outcome mRS after 3 months. Likewise, we found no statistically significant difference between both groups concerning in-house mortality or mortality after 3 months, duration of ventilation or feasibility or safety of MT. However, we found a significant difference between the treatment groups concerning the length of stay in hospital to the disadvantage of the experimental cohort (6.4 ± 5.0 vs. 4.5 ± 4.14 days; $p = 0.01$). We found a higher, but not statistically significant conversion rate from CS to GA in the KEEP SIMPLEST cohort (14 (20.3%) vs. 10 (14.5%); $p = 0.52$) (Table 3). The experimental group also showed a lower consumption rate of continuous analgesics (15.9% vs. 94.2%; $p < 0.001$). Consumption of sedatives (95.7% vs. 94.2%, $p = 1.0$) and norepinephrine were similar in both groups (49.3% vs. 35.3%, $p = 0.13$). The mean infusion rate and the total doses of each administered medication are summarized in the online supplement Tables 1 and 2. The incidence of critical hypo- and hypertension after MT was significantly lower in the experimental cohort (13% vs. 1.4%, $p = 0.013$). The individual rates of (critical) hyper- and hypotension are summarized in the online supplement Table 3.

An additional subgroup analysis on the directly admitted (and not from externally transferred) patients of the in-house workflow parameters (door-to-CT, door-to-first angiographic image and CT-to-first angiographic image) only showed a trend in the mean CT-to-first angiographic image time in favor of the experimental group, but without statistical significance (35.6 ± 20.5 min vs. 45.6 ± 18.5 min; $p = 0.06$) (online supplement Table 1).

Discussion

Utilizing KEEP SIMPLEST study to apply a new adjusted standardized protocol, patients with anterior circulation stroke receiving thrombectomy had an improved workflow of periinterventional management reflected by significantly reduced door-to-recanalization time as well as lower door-to- and CT-to-first angiographic image time. Our subgroup analysis of in-house patients who were not transferred from tertiary hospitals showed a 10-min decrease in the CT-to-first angiographic image time, even if the results were not statistically significant. These are important reductions in transfer and preparation times before MT. In particular, the CT-to-first angiographic image time reflects the time interval, which can be optimized by the organization and preparedness of the intensive care team, which would be instructed to start preparation for an MT when a CT scan and CT angiography had been performed. Despite those improvements in time to treatment, there was no improvement in neurological outcome from stroke.

The workflow analysis of the ESCAPE trial has demonstrated that every 30-min increase in the CT-to-recanalization time decreased the probability of achieving an independent outcome by 8.3% [17]. The Star study revealed that for every 1-h increase from stroke onset to recanalization, the odds ratio of a good clinical outcome decreased by 38% [18]. We therefore think that a reduction in the time from CT to first angiographic image by as little as 10 min (46 vs. 36 min) may be clinically relevant even if the differences were not significant in our analysis. Early neurological recovery defined as NIHSS reduction at 24 h and long-term clinical outcome determined by mRS after 3 months were similar in both groups. We did find a trend that more patients in the experimental group experienced a favorable outcome (20.2% vs. 31.3%) which could be the result of shorter times to recanalization and higher recanalization rates than in the SIESTA group. However, the results were not statistically significant, probably due to the small sample size.

Intraprocedural conversion rates from CS to GA due to complications such as respiratory distress or agitation were not significantly different in both sedation regimens used in the KEEP SIMPLEST and the SIESTA groups. Conversion from CS to GA did not result in worse clinical outcomes for patients in either group.

Only few studies have discussed or compared different drugs for sedation in CS for EST. One study reported dexmedetomidine combined with pentazocine as an effective sedative in 38 stroke patients receiving EST [19]. Another study compared CS using dexmedetomidine with patients who had received GA and found that the use was safe and reduced variations in blood pressure and use of vasopressors significantly when compared

Table 3 Workflow, interventional and clinical course, and outcome

Variable	SIESTA (N = 69)	KEEP SIMPLEST (N = 69)	Coefficient of regression model (95% CI)	p value
Primary outcome				
Improvement in NIHSS: mean (SD)	− 4.3 (7.7)	− 3.8 (10.5)	0.36 (− 2.31; 3.02)[a]	0.79
Secondary outcomes				
Clinical: no. (%)			− 0.24 (− 0.84; 0.35)[b]	0.42
mRS 0–2 after 3 months	14 (20.2)	21 (31.3)		
mRS 0–1 after 3 months	11 (15.9)	14 (20.9)		
mRS 0–3 after 3 months	33 (47.7)	35 (52.2)		
In-house mortality	4 (5.8)	9 (13)		0.27
Mortality after 3 months	17 (24.6)	14 (20.9)		0.68
Logistics: mean (SD)				
Length of stay in hospital [days]	4.5 (4.1)	6.4 (5.0)		0.01
Ventilation: yes (%)	10 (14.5)	14 (20.3)		0.52
Length of ventilation[d] (h)	48.8 (133.11)	49.4 (86.0)		0.99[e]
Door-to-groin (min)	65.3 (19.57)	65.7 (40.63)		0.94
Door-to-reperfusion (min)	156.8 (75.9)	128.6 (69.5)		0.02
Duration of EST (min)	131.9 (64.03)	92 (52.0)		<0.001
Feasibility of EST: no. (%)				
Degree of reperfusion (TICI)				0.19[c]
0–I	7 (10.1)	4 (5.8)		
IIa	7 (10.1)	3 (4.3)		
IIb	33 (47.8)	34 (49.3)		
IIc	0 (0)	9 (13)		
III	22 (31.9)	18 (26.1)		
Substantial patient movement	6 (8.7)	4 (5.8)		0.75
Difficult vascular approach	9 (13)	3 (4.3)		0.15
Other	7 (10.1)	8 (11.6)		1
Safety: no. (%)				
Complications before EST	3 (4.3)	10 (14.5)		0.07
Impaired monitor installation	0 (0)	1 (1.4)		1
Difficulties of venous puncture	1 (1.4)	1 (1.4)		1
Other complications	1 (1.4)	7 (12.8)		0.008
Complications during EST	8 (11.6)	5 (7.2)		0.546
Critical hyper- or hypotension	0 (0.0)	3 (4.3)		0.25
Critical ventilation or oxygenation disturbance	3 (4.3)	0 (0)		0.25
Necessity of intubation	10 (14.5)	14 (20.3)		0.52
Intervention-associated complications	2 (2.9)	0 (0)		0.48
Vessel perforation with ICH and/or SAH	2 (2.9)	0 (0)		0.48
Other complications	0 (0)	3 (4.3)		0.25
Complications after EST	5 (7.2)	10 (14.5)		0.15
Hyper- or hypotension[f]	9 (13)	1 (1.4)		0.013
Hyper- or hypothermia[g]	7 (10.1)	9 (13)		0.79
Delayed extubation[h]	4 (5.8)	4 (5.8)		1.0
Ventilation-associated complications	2 (2.9)	0 (0)		0.48
Pneumonia	2 (2.9)	4 (5.8)		0.68

EST endovascular stroke treatment, *ia* intra-arterial, *ICH* intracerebral hemorrhage, *iv* intravenous, *KEEP SIMPLEST* KEep Evaluating Protocol Simplification In Managing Periinterventional Light Sedation for Endovascular Stroke Treatment, max maximum, min minimum, *mRS* modified Rankin Scale, *N* number, *NIHSS* National Institutes of Health Stroke Scale, *SAH* subarchnoidal hemorrhage, *SD* standard deviation, *SIESTA* Sedation versus Intubation for Endovascular Stroke TreAtment, *TICI* thrombolysis in cerebral infarction

[a] Linear mixed effects model

[b] Proportional odds logistic regression

[c] p value for dichotomization TICI 0-IIa and IIb-III

Table 3 (continued)

[d] Lower sample size (10 patients in the SIESTA and 14 in the KEEP SIMPLEST cohort were converted from CS to GA)

[e] Unpaired t test for ventilated patients only

[f] Blood pressure > 180 mmHg or < 120 mmHg

[g] Temperature > 37.2 °C or < 36.0 °C

[h] Presepcified as extubation > 2 h after cessation of analgosedation

with the GA group [20]. Dexmedetomidine is a sedative with an analgesic component, which makes it a very suitable drug for the periinterventional management during EST. We are not aware of any other studies that have described the systematic combination of propofol and esketamine in patients receiving EST. However, that combination, even as a true mixture ("ketofol"), has been used in other settings and has a good safety profile [21]. The advantages associated with the use of propofol include a lower incidence of nausea and vomiting, quick recovery and the ability to decrease intracranial pressure, cerebral blood flow and cerebral metabolic rate for oxygen, as well as other potential neuroprotective effects [22]. However, propofol can also decrease cardiac output and cause bradycardia, hypotension, hypoventilation and lactate acidosis, all of which are undesirable side effects in periinterventional management of stroke patients [23].

The use of esketamine in patients presenting with acute stroke may offer several advantages. In addition to being a sedative, esketamine has analgesic properties which may decrease the use of analgesics, particularly opioids. Additionally, it has been suggested in several studies that esketamine may have neuroprotective effects even if scientific data on the subject are limited [24]. More than 80% of patients in the experimental group did not require any additional i.v. analgesic. Additional attributes of esketamine are proposed neuroprotective effects as well as bronchodilatory, antihyperalgesic and antiepileptic effects [25]. The most important property is probably that esketamine is a sedative without hypotensive effects. This could be demonstrated in the KEEP SIMPLEST study, as patients treated with low-dose propofol combined with esketamine had a lower incidence of critical hypo- and hypertension after MT than patients treated with propofol and remifentanil in SIESTA. Typical side effects of ketamine such as hallucinations or delirium, which are believed to be less frequent in esketamine than in ketamine, should not be underestimated even though these were not observed in our study. Potential adverse events such as laryngospasm and hypersalivation are rare [26].

Our results have demonstrated the feasibility and safety of a more streamlined protocol, changes in periinterventional equipment and the combination of propofol and esketamine for effective CS in patients receiving EST. Complication rates before MT were slightly higher in the experimental group than in the control group. However, this was mostly due to thrombosis of the femoral arteries, fits of coughing or anaphylactic reactions to contrast agent probably without association with the new SOP.

The greatest limitation of our study was the relatively small population which may explain why differences between both groups were not always significant. The limited sample size and standard deviations measured in both groups for the CT-to-first image time seem to be the primary reason why some differences between the KEEP SIMPLEST and the SIESTA groups may not have been statistically significant. Also, not every patient from the CS group of the SIESTA trial could be matched with a partner in the KEEP SIMPLEST group, which resulted in a reduction in the maximal possible sample size of 74 patients per group. Furthermore, our SOP has been designed for and adjusted to the conditions at Heidelberg University Hospital and the single-center nature of this study therefore limits its generalizability. Permanent members of our NICU team will also have benefitted from accumulated experience since the SIESTA trial was completed in 2016 with considerable increase of EST rates since then. Finally, an important limitation is the fact that an increasing number of patients were transferred to our center from tertiary hospitals for EST in the KEEP SIMPLEST group compared to the SIESTA group. This has certainly resulted in significantly reduced door-to-groin times in transferred patients, because the decision for EST had already been made before admission. This further reduced the sample size for sensitivity analyses and may have led to in-house workflow improvements not having such a strong impact.

In our opinion, the most relevant result of KEEP SIMPLEST is the significant reduction in in-house delays, most notably the CT-to-first angiographic image time and the demonstration of safety and feasibility of our new SOP and sedation regimen. These factors contributed to a significant reduction in our door-to-reperfusion time, and this has the potential to transduce into better clinical outcomes in a larger patient cohort.

Conclusion

Our results suggest that a standardized, continuously optimized SOP can significantly reduce treatment times and decrease in-house delays in patients receiving EST, without compromising safety. We demonstrated the safety and effectiveness of our new SOP. Streamlining and standardization of treatment processes can further

reduce door-to-reperfusion time. This is also the first study which has demonstrated that a standardized sedation regimen with esketamine and propofol is safe and feasible in patients receiving MT while reducing the use of opioids and blood pressure variability.

Electronic supplementary material
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Author Contributions
SS designed the study protocol, organized the trial, screened and recruited study subjects, collected and interpreted data, did the literature research, and wrote the manuscript. DW did the statistical analysis, created tables, and wrote the statistical analysis section of the manuscript. MU collected and interpreted data, did the literature research, and wrote the manuscript. WW helped with study design, implementation and realization of the trial, interpreted data, planned the manuscript structure and critically reviewed the manuscript. JP, SS and PH collected data and critically reviewed the manuscript. LU helped with design of the statistical analysis and the statistical section of the manuscript and reviewed the manuscript. MM and MB contributed neuroradiological components to the study design, interpreted data, and critically reviewed the manuscript. PAR contributed to implementation and conduct of the trial, screened study subjects, interpreted data and critically reviewed the manuscript. MK provided the biostatistical contribution to the protocol, wrote the statistical analysis plan, organized statistical data analysis, wrote the statistical analysis section of the manuscript and critically reviewed the manuscript. JB had the idea for the trial, designed the study protocol, planned, prepared, organized, supervised the trial, screened study subjects, interpreted data, did the literature research and wrote the manuscript.

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Conflicts of Interest
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Ethical Approval
The corresponding author confirms the adherence to ethical guidelines, and the trial was approved by our institutional review board (Ethikkommission Medizinische Fakultät Heidelberg, ID S-325/2015).

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