Stroke-Related Early Tracheostomy Versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT)

A Randomized Pilot Trial

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Background and Purpose—Optimal timing of tracheostomy in ventilated patients with severe stroke is unclear. We aimed to investigate feasibility, safety, and potential advantages of early tracheostomy in these intensive care unit (ICU) patients.

Methods—This prospective, randomized, parallel-group, controlled, open, and outcome-masked pilot trial was conducted in neurological/neurosurgical ICUs of a university hospital. Patients with severe ischemic or hemorrhagic stroke and an estimated need for at least 2 weeks of ventilation were randomized to either early tracheostomy (within day 1–3 from intubation; early) or to standard tracheostomy (between day 7–14 from intubation if extubation could not be achieved or was not feasible; standard). The primary outcome was length of stay in the ICU; secondary outcomes were diverse aspects of the ICU course.

Results—Sixty patients were randomized and analyzed. No differences were observed with regard to the primary outcome length of stay in the ICU (median 18 [interquartile range 16–28] versus 17 [interquartile range 13–22] days, median difference: 1 [−2 to 6]; P=0.38) or to most secondary outcomes, including adverse effects. Instead, use of sedatives (62% versus 42% of ICU stay, median difference 17.5 [3.3–29.2]; P=0.02), ICU mortality (ICU deaths 3 [10%] versus 14 [47%]; P<0.01) and 6-month mortality (deaths 8 [27%] versus 18 [60%]; P=0.02) were lower in the early group than in the standard group, respectively.

Conclusions—Early tracheostomy in ventilated intensive care stroke patients is feasible, and safe, and presumably reduces sedation need. Whether the suggested benefits in mortality and outcome truly exist has to be determined by a larger multicenter trial.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT01261091. **(*Stroke*. 2013;44:21-28.)**

Key Words: airway ■ critical care ■ intensive care ■ intubation ■ stroke ■ tracheostomy ■ ventilation

The prognosis for stroke patients requiring mechanical ventilation is poor, with mortality ranging between 40% and 80%.[1–5] Optimizing airway management to translate into better clinical outcome is therefore of great importance.

If critical care patients require long-term ventilation, a tracheostomy (TT) is customarily performed. Acknowledged advantages of a short tracheal cannula compared with a long orotracheal tube include less airway dead space and thus less work of breathing, oropharyngeal and laryngeal lesions are avoided, nursing care is facilitated, and patient comfort is increased.[6,7] However, TT can lead to short-term complications such as pneumothorax, damage to the trachea and adjacent organs, bleeding and infections, as well as more long-term disadvantages related to an indwelling artificial airway. It is widely agreed that TT should be performed as soon as its need becomes obvious, but how this need is determined remains controversial and optimal timing of TT is thus unclear.[7] The procedure, either percutaneous or surgical, is commonly performed after 2 to 3 weeks from intubation, often after extubation attempts have failed.

However, previous randomized trials in selected non-neurological intensive care unit (ICU) populations have suggested that early TT is associated with advantages such as fewer ICU complications, less need for analgesics and sedatives, shorter duration of ventilation, shorter length of ICU stay, and—in 1 trial—even lower mortality.[8,9] On the other hand, studies in large, mixed ICU populations were largely disappointing.[8,10] Although some promising retrospective data exist for early TT in neurological ICU patients,[11–14] these only emerged as subgroups in other trials or studies on head trauma.[15–20] The question has never been addressed prospectively for ventilated stroke patients thus far.

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Here, we have conducted a randomized pilot trial to investigate the safety, feasibility, and potential benefits of early TT compared with prolonged intubation in ventilated stroke patients.

Methods

SETPOINT (Stroke-related Early Tracheostomy vs. Prolonged Orotracheal Intubation in Neurocritical care Trial) is a registered prospective, investigator-initiated, randomized, open, outcome-masked, single-center trial. Patients were recruited in the neurological and neurosurgical ICUs of our university hospital between August 2009 and April 2011. The detailed trial protocol was published previously[8] and is briefly summarized in the following.

Patients

Inclusion criteria were as follows: (1) Age of at least 18 years, (2) admission to neurological and neurosurgical ICUs, (3) diagnosis of nontraumatic intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), or acute ischemic stroke (AIS), (4) intubated and expected need of mechanical ventilation support for at least 2 weeks, as based on a non-validated in-house assessment score[8] and the judgment of 2 experienced neurological intensive care specialists, and (5) written informed consent by the legal representative. Patients were excluded if they (1) had already been ventilated for >3 days, (2) had severe chronic cardiopulmonary comorbidities, (3) presented with anatomical (neck tumor, large struma, etc) or clinical (severe pulmonary failure, intracranial pressure crises, etc) conditions that would have jeopardized percutaneous dilational tracheostomy (PDT), (4) were expected to require a permanent surgical tracheostomy (ST; such as in cases of very extensive brainstem lesions), (5) were enrolled in any other intervention trial, (6) had a life expectancy of <3 weeks, or (7) were pregnant. Baseline scores were assessed on admission in the emergency room or during the first 24h after enrolment (ie, on day 1 or 2 after admission).

The trial was approved by the local ethics committee (Ethikkommission Medizinische Fakultät Heidelberg, ID-code S-060/2009) and conducted in accordance with the Declaration of Helsinki.

Procedures

Simple randomization was done using opaque, sealed envelopes for masking prepared by a trial-independent person and based on a computer-generated randomization list. Patients allocated to early TT received a PDT within 3 days from intubation. Patients allocated to the standard group received a PDT between day 7 and 14 from intubation if extubation, although aimed for, was not possible until then.

PDT is an established method of cannulating the trachea below the thyroid cartilage.[21] In SETPOINT, a modified version of the Ciaglia method was applied, using bronchoscopy and a Smiths Medical Ultra Perc tracheostomy kit as described previously.[8] However, if unforeseen conditions after randomization rendered primary ST or conversion from PDT to ST necessary, this was performed by the ENT surgeons at the bedside as soon as possible in customary fashion[22] and did not lead to exclusion from the trial. All PDTs were performed by neurological and neurosurgical ICU intensivists trained and supervised by the senior author.

ICU management for both trial groups was based on in-house protocols and general guidelines[8] to achieve fair homogeneity between groups.

The primary end point was intensive care unit length of stay (ICU-LOS), because this was repeatedly demonstrated in trials on early TT in non-neurological ICU patients and considered of high importance with regard to an early start of neuro-rehabilitation. Secondary end point were duration of ICU dependence, functional outcome (according to the modified Rankin Scale at discharge and at 6 months from admission), mortality and cause of death (during the ICU stay or within 6 months from admission), duration of ventilation, duration and quality of respirator weaning, level of sedation, duration of analgesia and sedation, duration of antibiotic treatment, occurrence of sepsis, number and type of TT-related complications, feasibility of decannulation in the course, and costs of treatment. Predefined serious adverse events were death, sepsis, and the TT procedure-related complications bleeding, malpositioning, pneumothorax, and emphysema.

It was not possible to blind the treating medical team to the intervention. However, long-term mortality and functional outcome were adjudicated by an investigator masked to patient and TT time point, based on narratives from a separate telephone interview. ICU mortality and cause of death were additionally confirmed by an independent investigator from charts and reports in which information on airway management was concealed.

Statistical Analysis

This pilot trial was planned to investigate feasibility and safety in the first place, and to generate a base for a multicenter follow-up trial a sample size of 60 patients (30 patients per group) was chosen (for reasons of single-center practicability and estimating a power of at least 60% when relating to effect sizes suggested in previous trials on early TT in non-neurological patients[9]; for details see protocol publication.)[8] Statistical measures where thus kept to a minimum. The analysis was done on the basis of the full-analysis-set. All patients were included in the analysis in the groups to which they were originally assigned.

The primary end point ICU-LOS was described using nonparametric methods (median; inter quartile range [IQR]), and the difference of medians was calculated by the Hodges-Lehmann estimator. Because of a substantial number of deaths during the ICU-stay, the median time until discharge from ICU (primary end point ICU-LOS) was also calculated by Kaplan–Meier analysis, where patients who died on ICU were treated as censoring events. Kaplan–Meier curves of ICU-LOS and survival times are displayed. Groups were compared using a log rank test and pointwise 95% confidence intervals (CI) for median discharge time as well as discharge or survival probability, respectively, were calculated.[23,24] Secondary outcomes were analyzed descriptively by tabulating the empirical distribution measures and calculating the associated 95% CI. *P* values for comparison of treatment groups are mainly descriptive. According to the scale level of the variables, mean, standard deviation or median, 1st and 3rd quartile, or absolute and relative frequencies are reported. Binary end points were analyzed with the χ^2 test; continuous end points were analyzed with the Wilcoxon test. Most variables were calculated as percentage of days on the ICU, or else defined otherwise in the respective legends. Data on weaning and Richmond Agitation Sedation Scale were summarized and the area under the curve (AUC) calculated by assessing the duration at the highest stage with the highest factor.

Furthermore, we performed an explorative analysis using Cox proportional hazards regression and taking time to death on the ICU as the dependent variable and treatment group as the main predictor variable. To adjust for potential confounders, age at baseline, National Institute of Health Stroke Scale (NIHSS) score, and Acute Physiology And Chronic Health Evaluation II (APACHE II) were included as continuous factors in a multivariate model. Hazard ratios and 95% CI (unvivariate and multivariate) are given.

The homogeneity of the treatment groups is described by comparing the demographic data and the baseline values. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Of 60 included patients, 1 patient randomized to early TT crossed over to the standard group for anatomical reasons that required ST and as a result of an organizational delay for the ST procedure. This cross-over constituted the only major protocol violation of the trial. Short-term outcomes were acquired with a fairly low rate of missing data (given in the tables).

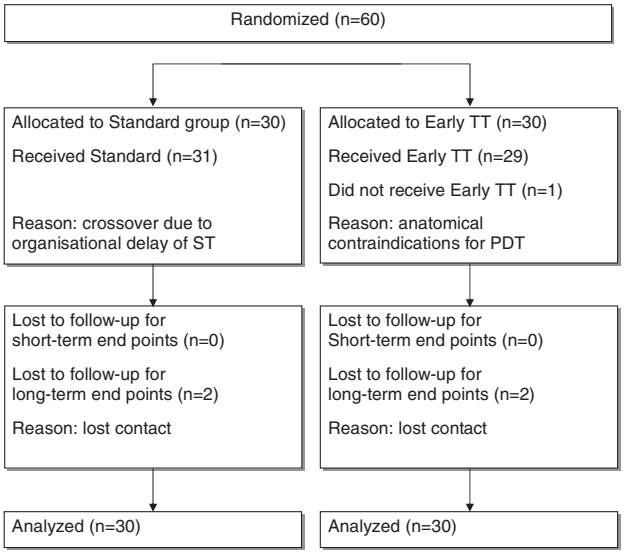

Figure 1. Stroke-Related Early Tracheostomy Versus Prolonged Orotracheal Intubation in Neurocritical Care (SETPOINT) Trial study flow chart.

Regarding assessment of long-term outcome, 2 patients of each group were lost to follow-up (Figure 1).

Baseline and clinical characteristics of the patients were well balanced in the treatment groups (Table 1).

Table 1. Baseline and Clinical Characteristics

	Standard (n=30)		Early TT (n=30)	
Demographics				
Female	10	(33%)	10	(33%)
Age	61	(13)	61	(12)
Clinical features				
SET score	13	(11–16)	13	(10–14)
GCS score	8	(5–10)	9	(7–11)
NIHSS score	20	(11–33)	21	(15–23)
Missing			1	
APACHE score	16	(11–19)	17	(13–19)
APS score	12	(8–15)	12	(10–14)
mRS score	4	(3–4)	4	(4–5)
Diagnosis				
ICH	13	(3%)	13	(43%)
Volume>25 mL	9	(30%)	8	(27%)
Missing			5	
Size (mL)	53	(51)	42	(33)
Missing			1	
AIS	9	(30%)	11	(37%)
Supratentorial, 2/3 MCA	6	(20%)	6	(20%)
Infratentorial	2	(7%)	2	(7%)
SAH	8	(27%)	6	(20%)
HH	5	(3–5)	3	(3–5)
Missing			1	
WFNS	5	(3–5)	4	(3–5)
Missing			1	
Location				
Supratentorial	25	(83%)	26	(87%)
Complications				
Additional IVH	17	(57%)	14	(50%)
Missing			2	
Graeb score	7	(4–10)	8	(6–10)
Hydrocephalus	21	(70)	19	(66%)
Missing			1	
Neurosurgical operation	15	(52%)	10	(35%)
Missing	1		1	
Airway management				
TT-type				
PDT	16	(95%)	27	(90%)
ST	2	(5%)	3	(10%)
None*	12		0	
Time to TT (from intubation)*,**	10.5	(9–11)	3	(3-3)
TT survivors	13	(43%)	22	(73%)
Decannulation in course				
Successful decannulation	10	(33%)	18	(60%)
Dead / no decannulation	2	(7%)	4	(13%)
Missing	6		8	
Not applicable*	12	(40%)	0	
Observation time (months)	6.6	(6.5–13.4)	7.5	(6.4–16.6)

Data are n (%), mean (SD) or median (lower – upper quartile).

TT indicates tracheostomy; ICH, intracerebral hemorrhage; AIS, acute ischemic stroke; SAH, Subarachnoid hemorrhage; SETscore, Stroke-related Early Tracheostomy score; GCS, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke Scale; APACHE II, Acute Physiology And Chronic Health Evaluation II; APS, Acute Physiology Score; mRS, modified Rankin Scale; MCA, middle cerebral artery; HH, Hunt and Hess; WFNS, World Federation of Neurosurgeons; IVH, intraventricular hemorrhage; PDT, percutaneous dilational tracheostomy; and ST, surgical tracheostomy.

*12 patients of the standard group died before TT (not included for analysis of time to TT and decannulation).

**1 patient of the early TT group switched treatment arm and was intubated at day 12 (not included). Missing: Data in the indicated number of patients was missing or could not be assessed reliably.

Distribution of admission diagnoses was 13 versus 13 for ICH, 8 versus 6 for SAH, and 9 versus 11 for AIS between the standard and the early group, respectively (Table 1).

We found no differences in the primary end point ICU-LOS (median 18 days [IQR 16–28] versus 17 days [IQR 13–22], median difference: 1 day, 95% CI, −2 to 6; P=0.38, Figure 2a and Table 2) or in most secondary end points between the groups (Table 2). Minor, procedure-related complications developed in 2 patients in the standard and 1 patient in the early group, but they did not have any obvious relevance for the clinical course (Table 2). However, use of sedatives was higher (62% vs 42% of ICU stay, median difference 17.5,

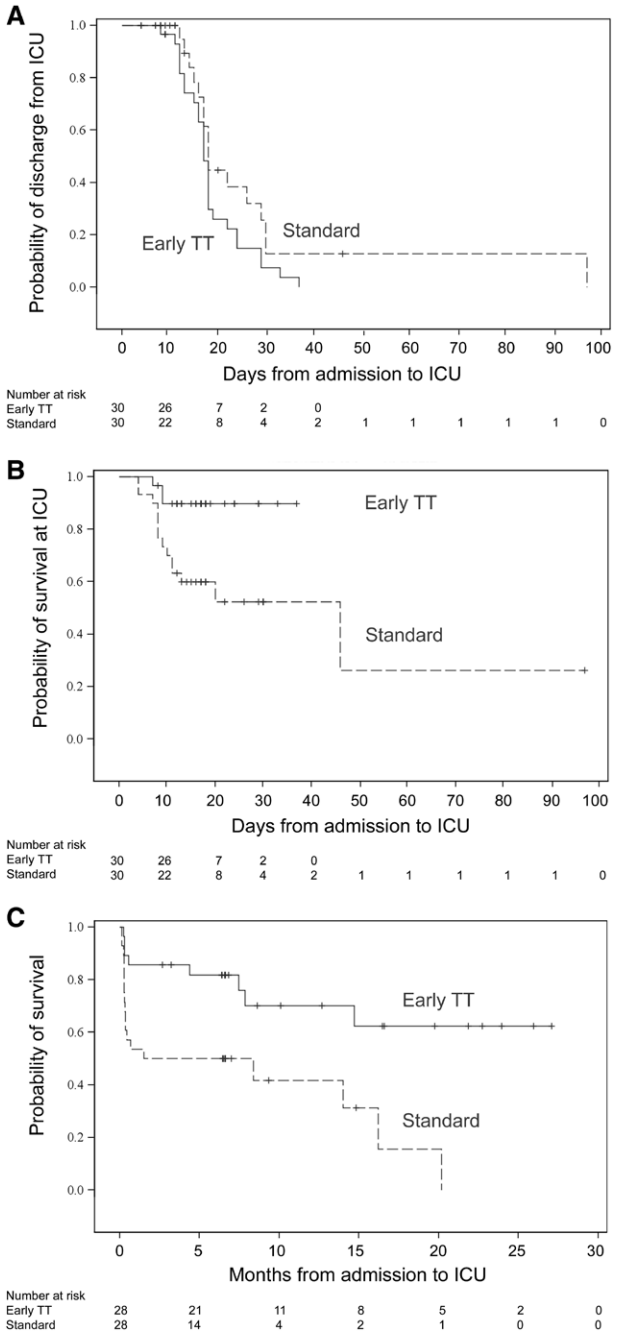

Figure 2. Kaplan–Meier estimates of time to discharge from ICU and time to death of patients randomized for Early TT or for Standard. **A**, Time to discharge from ICU (death is censored; median observation time 18 days; Probability of discharge from ICU at 18 days: Early TT 30% (95% CI, 13 to 47), Standard 45% (22 to 68); logrank test: χ^2= 2.934, *P*=0.087. **B**, Time to death on ICU (discharge is censored; median observation time 18 days; survival probability at 18 days: Early TT 90% (95% CI, 79 to 100), Standard 60% (42 to 77); logrank test χ^2= 7.589, *P*=0.006). **C**, Time to death (survival probability at 6 months after admission: 82%, 95% CI, 67 to 96) or for Standard (50%, 95% CI, 31 to 69); logrank test: χ^2= 9.932, *P*=0.002). The horizontal line (in **A** and **B**) represents 1 patient in the standard group who was discharged from ICU after 97 days. ICU indicates intensive care unit; TT, tracheostomy.

95% CI, 3.3 to 29.2; *P*=0.02) and use of opioids trend-wise or in tendency higher (75% vs 64% of ICU stay, median difference 10.1, 95% CI, −2.5 to 22.7; *P*=0.08) in the standard group than in the early group. Furthermore, the Richmond Agitation Sedation Scale was higher over a longer period (AUC 480 vs 402; median difference 67.4, 95% CI, 17 to 117; *P*<0.01), reflecting a less deep sedation level, and more time was spent under assisted (as opposed to fully controlled) ventilation mode (28% versus 12%; median difference 10.2, 95% CI, 0 to 20.3; *P*=0.05) in the early TT group.

ICU mortality was higher in the standard than in the early TT group, at 14 (47%) versus 3 (10%) deaths, respectively (rate difference 36.7% [17.6–55.7%]; *P*<0.01; Figure 2b). ICU death was predominantly related to refractory brain injury complications such as rebleeding, vasospasms or secondary infarctions (depending on the primary pathology), eventually leading to intractable increases in intracranial pressure (ICP) and herniation (Table 3). Six months after admission, mortality remained higher in the standard than in the early group (18 versus 8 deaths, rate difference 35.7% [15–56%]; *P*=0.02; Figure 2c). Poor functional outcome (ie, modified Rankin Scale of 5–6) was found more frequently in the standard group (71% versus 46%, rate difference 25.0% [5–45%]; *P*=0.06). Cox proportional hazards regression analysis showed a reduced risk of ICU mortality for early TT compared with standard treatment even when adjusted for age and the severity scores NIHSS and APACHEII (hazard ratio, 0.18; 95% CI, 0.05 to 0.63; *P*=0.01; Table 4).

Discussion

This randomized pilot trial in cerebrovascular neurocritical care patients demonstrates feasibility of early tracheostomy as compared with prolonged intubation and suggests safety. Except for differences in the need for sedatives, in the level of sedation and the mode of ventilation, no other relevant benefits regarding the ICU course were detected, particularly not regarding length of stay, the primary outcome of the trial. Although the trial suggests mortality and outcome benefits in favor of early tracheostomy, this has to be regarded with great caution given the small sample size.

Previous retrospective studies suggested that ventilated neurological ICU patients might particularly benefit from early tracheostomy: In a retrospective subgroup analysis of 129 mixed ICU patients, the 31 neurological/neurosurgical patients could be weaned fastest from the ventilator after TT compared with other subgroups.[12] Another retrospective study in 97 patients with ICU-dependent AIS, ICH, or SAH showed that stroke survivors in whom long-term ventilation culminated in TT had a favorable outcome in about 25% of the cases and a shorter length of stay on the ICU if TT was performed early.[13] The latter was likewise demonstrated in a restrospective study on 69 ventilated stroke patients with infratentorial lesions.[11] A fourth retrospective analysis in 28 ICU patients with quite heterogeneous nontraumatic brain injuries even suggested lower mortality through early TT.[14]

Tracheostomies are increasingly being performed by neurological intensive care physicians (as opposed to surgeons) at the bedside quickly, at low cost and with low complication rates,[25] as the percutaneous technique has become equivalent,

Table 2. Primary and Secondary Outcomes of ICU Course

	Standard		Early TT		Median Difference (95% CI)		*P* Value*
Survivors, n	16		27				
ICU-LOS, d	18	(16-28)	17	(13-22)	1	(–2 to 6)	0.38
ICU-need, d	16	(14-22)	14	(11-18)	3	(–1 to 7)	0.18
Ventilation time, d	12	(8-16)	15	(10-17)	2	(–1 to 5)	0.23
Ventilation mode							
Fully controlled	70	(53-87)	53	(41-79)	–9.4	(–23.5 to 4.6)	0.18
Assisted	12	(0-32)	28	(14-39)	10.2	(0.0 to 20.3)	0.05
Spontaneous	3	(0-10)	6	(1-16)	2.5	(0.0 to 7.2)	0.07
Weaning phases,** n	29		30				
S1	49	(30-74)	33	(16-58)	15	(–1 to 31)	0.10
S2	8	(0-26)	6	(0-13)	0	(–1 to 9)	0.50
S3	8	(0-16)	12	(6-21)	–3	(–8 to 1)	0.18
S4	0	(0-11)	6	(0-18)	0	(–8 to 0)	0.25
S5	11	(0-20)	16	(6-30)	–7	(–16 to 0)	0.05
S6	2	(0-8)	5	(0-11)	0	(–5 to 0)	0.54
Weaning-AUC	71	(55-88)	69	(50-101)	3	(–18 to 21)	0.97
Sedation level							
RASS**(n)	29		30				
–5	18	(3-63)	19	(0-35)	3.3	(–5.5 to 18.2)	0.33
–4	33	(13-56)	22	(15-36)	8.4	(–4.2 to 22.2)	0.18
–3	11	(0-18)	12	(0-27)	0	(–11.1 to 4.1)	0.68
–2	0	(0-7)	14	(0-24)	–9.2	(–16.7 to –1.8)	<0.01
–1	0	(0-2)	0	(0-9)	0	(–2.8 to 0)	0.15
0	0	(0-7)	0	(0-0)	0	(0 to 0)	0.38
RASS-AUC	480	(416-543)	402	(329-483)	67.4	(17 to 117)	<0.01
Drugs							
Antibiotics (29/30)	75	(59-88)	67	(54-77)	6.9	(–5.6 to 17.6)	0.25
Opioids (28/30)	75	(58-86)	64	(44-78)	10.1	(–2.5 to 22.7)	0.08
Sedatives (29/29)	62	(45-75)	42	(28-55)	17.5	(3.3 to 29.2)	0.02
Total costs of treatment (€)	30 546	(17 352-12 1075)	29033	(10 291-68 124)	2874	(–4598 to 18 889)	0.24
Daily costs of treatment (€)	1745	(1660-1860)	1760	(1707-1845)	–20	(–205 to 148)	0.77
Patients with complications, n**							
Sepsis	13/30	(43%)	15/30	(50%)			0.60
TT-related (any)	2/18	(11%)	1/30	(3%)			0.28
Bleeding	2/18	(11%)	0				
Malpositioning	0		1/30	(3%)			
Pneumothorax	0		0				
Emphysema	0		1/30	(3%)***			

Data are median (lower – upper quartile), median difference (Hodges-Lehmann estimator), and 95% confidence intervals, data presented as % of ICU-stay if not otherwise stated.

AUC indicates area under the curve; ICU-LOS, intensive care unit length of stay; RASS, Richmond Agitation Sedation Scale, –5 deeply sedated to 0 awake and calm, higher values were not recorded; TT, tracheostomy; and Weaning phases S1 (fully controlled ventilation), S2 (fully AND any assisted mode ventilation), S3 (controlled / assisted AND <16h CPAP (continuous positive airway pressure) ventilation/day), S4 (controlled / assisted AND >16h assisted CPAP ventilation/day), S5 (CPAP ventilation AND <16h spontaneous breathing/day), S6 (CPAP ventilation AND > 16h spontaneous breathing/day).

Weaning, RASS: number of patients in standard group n=29, missing data for 1 patient.

Drugs: Exposition time as % of days on ICU with medication, number of patients given in brackets (early TT/standard).

* Wilcoxon test.

**Complications: In the standard group 12 patients died before TT, therefore reporting of TT-related complications was not applicable.

***Emphysema and malpositioning occurred in the same patient.

if not more advantageous,[26] to surgical techniques.[21] Safety of the procedure was further supported by our trial, resulting in very few TT complications that were, more importantly, of low clinical relevance.

Feasibility was demonstrated in that the protocol could be applied in all 60 patients, with organizational problems delaying TT in 1 patient only. Single-center recruitment of 60 patients could be realized in a reasonable time period of 2 years.

Table 3. Mortality and Functional Outcome

	Standard		Early TT				
	n=30		n=30		Difference (95% CI)		*P* Value
Deaths							
ICU	14/30	(47%)	3/30	(10%)	36.7%	(17.6 to 55.7%)	<0.01
CNS-related	10	(37%)	3	(10%)			
Extensive primary brain lesion, refractory ICP, herniation	1		0				
Secondary brain lesion, refractory ICP, herniation	9		3				
Not CNS-related	3	(10%)	0	(0%)			
Pulmonary embolism	1		0				
Cardiopulmonary failure after therapy withdrawal	2		0				
Unclear	1		0				
POST-ICU (up to 6 months)	4/28	(14%)	5/28	(18%)			
Circulatory failure	4		4				
Ileus			1				
All deaths	18/28	(64%)	8/28	(29%)	35.7%	(15.4 to 56.0%)	0.02
Functional Outcome							
mRS at discharge from ICU							
0-4	0		0				
5-6	30	(100%)	30	(100%)			
mRS 6 months from admission*							
0-4	8	(29%)	15	(54%)			
5-6	20/28	(71%)	13/28	(46%)	25.0%	(5.0 to 45.0%)	0.06
mRS 6 months from admission*							
2	0	(0%)	2	(7%)			
3	2	(7%)	4	(13%)			
4	6	(20%)	9	(30%)			
5	3	(10%)	5	(17%)			
6	17	(57%)	8	(27%)			
Median mRS	6	(4-6)	4	(4-6)			

Data are n (%), absolute rate differences between the groups and 95% confidence intervals for the differences.

CI indicates confidence interval; CNS, central nervous system; ICU, intensive care unit; mRS, modified Rankin Scale; and TT, tracheostomy.

*Information on the status 6 months after the treatment was not available for 2 patients of each group (rate of all deaths was calculated based on the base of n=28 in each group)

Most potential advantages of early TT, particularly a reduction in ICU-LOS as suggested in trials from other ICU populations, were not found in our patients. Even with regard to a strictly defined period of ICU dependence, we only found a slight trend in favor of early TT. Some differences in ICU variables possibly could not be demonstrated because of the small sample size of this pilot trial and hence its low power; they might still exist. Alternatively, the dominating, severe cerebral disease might have prevented us from detecting differences in these short-term outcomes. We did find a significant reduction, however, in the use of sedatives and a trend for reduced use of opioids in the early TT group. This is a clinically important result, as the hazardous potential of these drugs has been demonstrated in numerous ICU studies.[27–31] This finding might also be reflected in the early TT patients spending less time in a fully controlled ventilation mode, which proposes additional pulmonary and weaning advantages. In any case, this pilot trial, despite its limited power, suggests that the effect size of these secondary outcomes as well as that of the primary outcome ICU-LOS is probably low in our population. We conclude that differences in ventilation time or ICU-LOS in dimensions of 8 or 15 days, respectively, as reported in previous trials in non-neurological ICU patients,[9] might not be achievable by early TT in stroke ICU patients.

We did not expect to find such a substantial difference in the ICU and long-term mortality between the groups. The observed mortality benefit prevailed over 6 months, and long-term analysis showed, at least trend-wise, a better functional outcome. Because 2 patients in each group were lost to follow-up and long-term outcome was assessed by telephone, however, these findings should be interpreted with caution. The mechanism underlying this survival benefit can hardly be derived from the other trial findings. The reduction in sedative and opioid use might indeed play a role, but should never be responsible for a difference in mortality of this dimension on its own. In particular, the mortality in the early group was exceptionally low. Therefore, we paid particular attention to detecting confounders such as illness severity and causes of death. Baseline features of the 2 groups, including clinical severity scores on admission, were generally well balanced.

Table 4. ICU Mortality: Exploratory Analysis of Potential Confounders

		Univariate			Multivariate		
Factor	n	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Treatment group							
Standard	30						
Early TT	30	0.179	0.051 – 0.624	0.007	0.180	0.052 – 0.628	0.007
Age	60	0.979	0.941 – 1.018	0.282	0.977	0.937 – 1.020	0.293
NIHSS	60	1.014	0.970 – 1.062	0.540	1.005	0.962 – 1.049	0.841
APACHE II	60	1.030	0.933 – 1.137	0.559	1.034	0.939 – 1.139	0.494

HR indicates hazard ratio. Treatment group = binary; age, NIHSS, APACHE II = measured at baseline, continuous factors.

Some parameters, however, such as mean size of ICH volume, ICH volume >25 mL, additional IVH, SAH frequency, SAH median Hunt and Hess, and need of neurosurgical interventions reflected a slightly more severe illness in the standard group, possibly explaining partially, but certainly not fully, the difference in mortality. Rather, we suspected that early TT might have rendered physicians and family more reluctant to decide on discontinuation of ventilation as part of therapy withdrawal in cases of unfavorable clinical courses. According to a masked observer who confirmed the causes of death, therapy withdrawal accounted for 2 of the 14 ICU deaths in the standard group, making this another possible contribution to the observed mortality difference. Next, a treatment bias cannot be completely ruled out in this open trial, although we applied strict protocols for all relevant aspects of ICU management, aiming for a homogeneous treatment in the 2 groups. Finally, in a trial of this size, and a patient population of this illness severity, small changes in the clinical course of the first days might considerably affect outcome and even render the observed difference in mortality, a chance finding. Thus, we remain skeptical with regard to our findings on outcome and mortality, mainly because we cannot convincingly correlate these with favorable findings in most other secondary outcomes. If a difference in mortality was indeed achievable by early TT, it would probably be of a much smaller effect size than observed here and be explained by a factor that we did not determine in our trial. For instance, we have noticed, but not analyzed systematically, that the ICP often decreased after TT, even though patients were sufficiently analgosedated before. Given the fact that the majority of patients eventually died of refractory ICP crises, we could hypothesize that ICP management after TT-related stress reduction might be more successful. This hypothesis, however, needs to be investigated prospectively in greater patient numbers.

Our trial has a number of limitations. First, the single-center design restricts generalizability. Second, the intervention naturally could not be masked from the caregivers, which might well have led to a treatment bias and resulted in differences of management and outcome. We tried to partially compensate for this by application of treatment protocols and adjudicator masking, but we cannot rule out relevant effects of these confounders. Third, the sample size was small and the patient population heterogeneous (ie, representing cerebrovascular disease in general rather than 1 major type of vascular pathology), possibly precluding statistical significance of some outcomes. In our reasoning, the size and location of the vascular lesion is more relevant for airway and ventilation compromise than the particular pathology type; additionally, the degree of heterogeneity was similar in both groups. Finally, although the trial suggests intruiging results in mortality and functional outcome, its design was that of a pilot trial, and as such not initially directed at outcome but rather at short-term ICU features. Thus, the methods for outcome assessment were not as standardized, detailed, and vigorous as what would be desirable.

Still, this is, to our knowledge, the first randomized trial conducted in this exceptionally burdened subgroup of stroke patients. The strengths of the trial are bias avoidance by randomization, standardization by implemented protocols, and masking wherever possible in this intervention setting.

In conclusion, we have demonstrated that early percutaneous tracheostomy in ventilated, severely ill patients with ischemic and hemorrhagic stroke is feasible and safe, and presumably reduces the need for sedatives. Whether benefits actually exist, that exceed a mere increase in survival and to also improve long-term functional outcome, needs to be investigated in a larger multicenter trial.

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Disclosures

None.

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