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ORIGINAL WORK

Mechanical Ventilation, Sedation and Neuromonitoring of Patients with Aneurysmal Subarachnoid Hemorrhage in Germany: Results of a Nationwide Survey

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Abstract

Objective: Current evidence-based guidelines for the management of aneurysmal subarachnoid hemorrhage (aSAH) focus primarily on timing, modality and technique of aneurysm occlusion, and on prevention and treatment of delayed cerebral ischemia. Significant aspects of management in the intensive care unit (ICU) during the later course of aSAH such as ventilation and sedation (VST) remain unaddressed. aSAH patients present unique challenges not accounted for in general ICU recommendations and guidelines, which is why we attempted to further characterize ICU practices in aSAH patients in Germany.

Methods: We conducted a nationwide survey on ICU practices in aSAH in Germany. Secondarily, we assessed the existence of and compliance with current guidelines regarding ICU practices. The questionnaire was designed in interdisciplinary fashion and distributed online through the kwiksurvey® platform (Bristol, UK).

Results: A total of 50 responses were received, accounting for a response rate of 49%. Twenty-one were university hospitals (UH), 23 high-volume centers (HVC), 6 low-volume centers (LVC). Half of the participating centers do not take into consideration WFNS at presentation to indicate ventilation. While 42% of centers rely on the *P/F* ratio to indicate ventilation, 62% of them have a cutoff value of < 200, and 38% of < 100. While most UH and HVC used propofol for the first phase of sedation (95%), LVC employed benzodiazepines (100%). Sedation deepening was done with ketamine in UH (75%) and HVC (60%), whereas LVC used predominantly clonidine (100%).

Conclusions: Our study clearly demonstrates that attitudes and practices pertaining to ICU management in aSAH are enormously heterogeneous, reflecting the lack of good quality evidence and differing interpretations thereof.

Keywords: Intensive care unit, Subarachnoid hemorrhage, Ventilation, Sedation

Introduction

Although mortality rates from aneurysmal subarachnoid hemorrhage (aSAH) declined over the past decades, case fatality remains high [1]. Evidence-based guidelines for the management of aSAH [2–5] focus primarily on the timing, modality and technique of aneurysm occlusion, and the prevention and treatment of DCI, while many of the problems encountered in the intensive care unit (ICU) during the later course of aSAH are unaddressed. Core aspects of ICU therapy, such as sedation and analgesia, and indication and targets of mechanical ventilation, must be considered and adapted for aSAH patients,

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for they are only addressed in general ICU recommendations and guidelines [6]. Although general principles apply for most ICU patients, aSAH patients can present unique challenges [3] not accounted for in these general recommendations and guidelines.

An international survey showed great treatment heterogeneity among centers treating patients with aSAH, particularly between North America and Europe, and between high-volume and low-volume centers [7]. A Scandinavian survey on sedation principles and monitoring techniques in patients with severe traumatic brain injury (TBI) and aSAH in neurocritical centers also revealed marked differences among the institutions analyzed [8]. Germany is no exception to the latter: a survey about contemporary management of aSAH revealed variance among centers, but most aspects interrogated pertained to aneurysm occlusion and postinterventional therapy [9].

Given the heterogeneity in practice and the lack of specific guidelines, it is important to better characterize how physicians are approaching intensive care management of aSAH patients, especially when it comes to ventilation and sedation therapy (VST), since these aspects are underappreciated in the literature. The hypothesis of this study is that aSAH treatment strategies most likely vary enormously from center to center. The aim of this study is to characterize the differences in neurocritical care (NCC) strategies of aSAH in Germany. To do so, we conducted a nationwide survey, evaluating distinct key treatment concepts during the ICU stay. We focus on the results of VST and neuromonitoring.

Materials and Methods

Since our aim was to analyze the differences and variability regarding the very basic but scientifically underappreciated treatment aspects of NCC in aSAH undertaken in Germany, we attempted to incorporate questions on indication, execution and treatment goals of VST. Also, current national and international guidelines were reviewed to assess the presence of recommendations on VST in aSAH. Based on these guidelines, a 70-question online survey was designed (kwiksurveys®, Bristol, United Kingdom) to determine NCC practices in aSAH in Germany. The questions were designed in interdisciplinary fashion, aiming to assess six categories of NCC: general department information, ventilation management, sedation management, perceived adverse events (AE) due to VST, monitoring, and surgical interventions during aSAH course. After the primary version of the questionnaire was done, we handed it out to two non-participating intensivists as a test run. After this, the questionnaire was slightly modified and finalized. The full questionnaire can be found in supplemental electronic material, SEM).

The survey was then distributed per e-mail to intensivists and neurosurgeons from 103 German hospitals. Institutions were primarily identified based on registration with the German Society of Neurological Surgery ("Deutsche Gesellschaft für Neurochirurgie", DGNC). Private practices and outpatient clinics were excluded. Individuals from the selected institutions were contacted based on their DGNC directory listing, prior personal communication with the senior author, or referral as the primary neurointensivist by the initially approached colleague. The questionnaire was online from June 2, 2017, to January 2, 2018. Follow-up e-mails were sent to non-respondents after 8 weeks. Institutional review board (IRB) approval was obtained. Implied consent was obtained by participating in the survey.

Institutions were categorized in: (a) academic/university hospitals (UH); (b) non-academic high-volume centers (HVC), with ≥ 30 aSAH/year; and (c) non-academic low-volume centers (LVC), with < 30 aSAH/year. ICU run by neurologists and/or neurosurgeons were considered "pure neuro", whereas ICU run by intensivists, neurosurgeons, and specialists from other non-neurological specialties were considered "interdisciplinary".

Responses are reported as percentage values of agreement/non agreement and were analyzed for statistically significant differences by means of Pearson's Chi Square test, assuming significance at a p value of less than .05 ($p \leq .05$) using SPSS® Statistics software package (SPSS® v.25, IBM®, Armonk, New York, United States).

Results

Existing VST Guidelines for aSAH

Current ICU management in Germany is guided by the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Association of the Scientific Medical Societies in Germany) [6] guidelines, in which ventilation goals and sedation recommendations are summarized. In these guidelines, some special remarks are made pertaining to NCC patients. Additionally, the Brain Trauma Foundation has issued comprehensive guidelines for the management of TBI patients [10], including ventilation and sedation in patients with intracranial hypertension (IHTN). In Table 1, we have summarized the recommendations pertaining to VST, and whether they mention aSAH patients.

Survey

A total of 50 responses were received, accounting for a response rate of 49%. Due to the length and plurality of the survey, we will report on and discuss the most

Table 1 Summary of VST recommendations according to national/German and international guidelines

Reference	Recommendation	Patient population
Ventilation		
AWMF [6]	Ventilation therapy should be indicated in patients with severe ARDS (Horowitz index < 100 mmHg)	Acute respiratory insufficiency
	Adapt ventilator settings to paO_2 60–80 mmHg/lowest possible FiO_2 in order to prevent pressure-induced lung injury	Acute respiratory insufficiency
	Consider/accept permissive hypercapnia ($paCO_2 > 45$ mm Hg) to reduce maximum ventilation pressure Limitation: elevated intracranial pressure	Acute respiratory insufficiency
TBI [12]	Normal ventilation is currently the goal in the absence of cerebral herniation and normal partial pressure of carbon dioxide in arterial blood ($paCO_2$) ranges from 35 to 45 mm Hg	Severe TBI
	Prolonged prophylactic hyperventilation with partial pressure of carbon dioxide in arterial blood ($paCO_2$) of 25 mmHg or less is not recommended	Severe TBI
Tracheostomy		
AWMF [6]	Patients with invasive ventilation therapy without predictable ventilation duration (and prolonged weaning) should undergo tracheostomy	Invasively ventilated patients
	No early tracheostomy in invasively ventilated patients	Invasively ventilated patients
TBI [12]	Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is felt to outweigh the complications associated with such a procedure	TBI
Monitoring		
AWMF [6]	Based on current data, no recommendations can be made for the use of a specific instrument to monitor analgesia or sedation in ICU patients with severe TBI and intracranial hypertension. Neurological exams should be performed routinely	TBI
IMCCMM [15]	All poor-grade SAH patients should be monitored and considered for multimodality monitoring	ASAH*
NCSMCC [3]	Monitoring of cardiac output may be useful in patients with evidence of hemodynamic instability or myocardial dysfunction	ASAH*
AHA/ASA SAH [2]	Monitoring volume status in certain patients with recent ASAH by some combination of central venous pressure, pulmonary wedge pressure, and fluid balance is reasonable, as is treatment of volume contraction with crystalloid or colloid fluids	ASAH*
Sedation		
AWMF [6]	Adequate analgesia and sedation according to a target RASS should be performed in the treatment of patients with severe TBI and/or IHTN	TBI
	Sedation regimes with propofol or midazolam are equally safe in patients with TBI. When prompt neurological examination is desired, propofol should be favored.	TBI
	Bolus doses of opioids (sufentanyl, fentanyl, alfentanil) should be administered in traumatic brain injury patients with IHTN only if the MAP is constantly monitored and maintained, because a significant drop in MAP and associated autoregulatory increase in CBV and ICP can otherwise occur	TBI
	A continuous intravenous administration of opioids (remifentanil, sufentanyl, fentanyl, morphine) in patients with IHTN should only be performed under continuous blood pressure monitoring	TBI
	Due to the favorable pharmacokinetics and thus possibility for rapid neurological evaluation, remifentanil should be preferred to other opioids for analgesia and sedation in neuro-trauma patients, provided conscious sedation will not be necessary for more than 72 h	TBI
TBI [12]	Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity	TBI
ESO [4]	No mention of sedation, except for its use in aneurysm surgery/endovascular intervention, and in patient transfer after ictus	ASAH*

Table 1 (continued)

Reference	Recommendation	Patient population
Sedation enhancement		
AWMF [6]	Ketamine-racemate should also be considered in patients with TBI and IHTN under controlled ventilation (constant $paCO_2$) and in addition to GABA-receptor agonist (blockade of excitatory potentials)	TBI
	Through the use of racemic ketamine (with its sympathomimetic and benign hemodynamic effects) a clinically relevant reduction of MAP and CPP can be avoided.	TBI
	Both racemic ketamine/midazolam-based or an opioid/midazolam-based sedation regimes can be used in mechanically ventilated traumatic brain injury patients with IHTN (no significant difference in effect on ICP, CPP)	TBI
	An S (+) -ketamine/methohexital-based and a fentanyl/methohexital-based sedation regime can be used equally safely (with respect to ICP and CPP) and effectively (regarding sedation achieved) in mechanically ventilated traumatic brain injury patients with intracranial hypertension	TBI
TBI [12]	High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy	TBI

*Denotes guidelines addressing ASAH

AHA/ASA American Heart Association/American Stroke Association, *ARDS* acute respiratory distress syndrome, *ASAH* aneurysmal subarachnoid hemorrhage, *AWMF* Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Association of the Scientific Medical Societies in Germany, *CBV* cerebral blood volume, *CPP* cerebral perfusion pressure, *ESO* European Stroke Organisation, *ICP* intracranial pressure, *IHTN* intracranial hypertension, *IMCCMM* international multidisciplinary consensus conference on multimodality monitoring, *MAP* mean arterial pressure, *NCSMCC* neurocritical care society's multidisciplinary consensus conference, *RASS* richmond agitation and sedation scale, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury

important findings. Because it was not mandatory to respond to all questions, some items have a lower response rate; this is stated whenever pertinent.

Generalizability and Representativeness

Twenty-one UH, 23 HVC and 6 LVC answered the questionnaire and thus constitute the sample. The answers of the participating centers represent 63% of the treatment volume of aSAH in Germany, based on an incidence of aSAH of 7.5/100.000/year and the aSAH caseload in the reporting institutions.

Hospital Characteristics

Most survey participants were HVC $n=23/50$ (46%) followed by UH $n=21/50$ (42%), and LVC $n=6/50$ (12%). In terms of ICU structure, most centers were led in interdisciplinary fashion (mixed-ICU; $n=42/50$ (84%), with pure neuro-ICUs $n=8/50$ (16%) being mostly represented in UH $n=5/8$ (62%), where they accounted for $n=5/21$ (24%) of all ICUs. Because of the great heterogeneity of the group sizes between interdisciplinary ICUs and neuro-ICUs, we refrained from making any further statistical analyses between these two groups to avoid type II error.

Ventilation Management and Indications for Tracheostomy

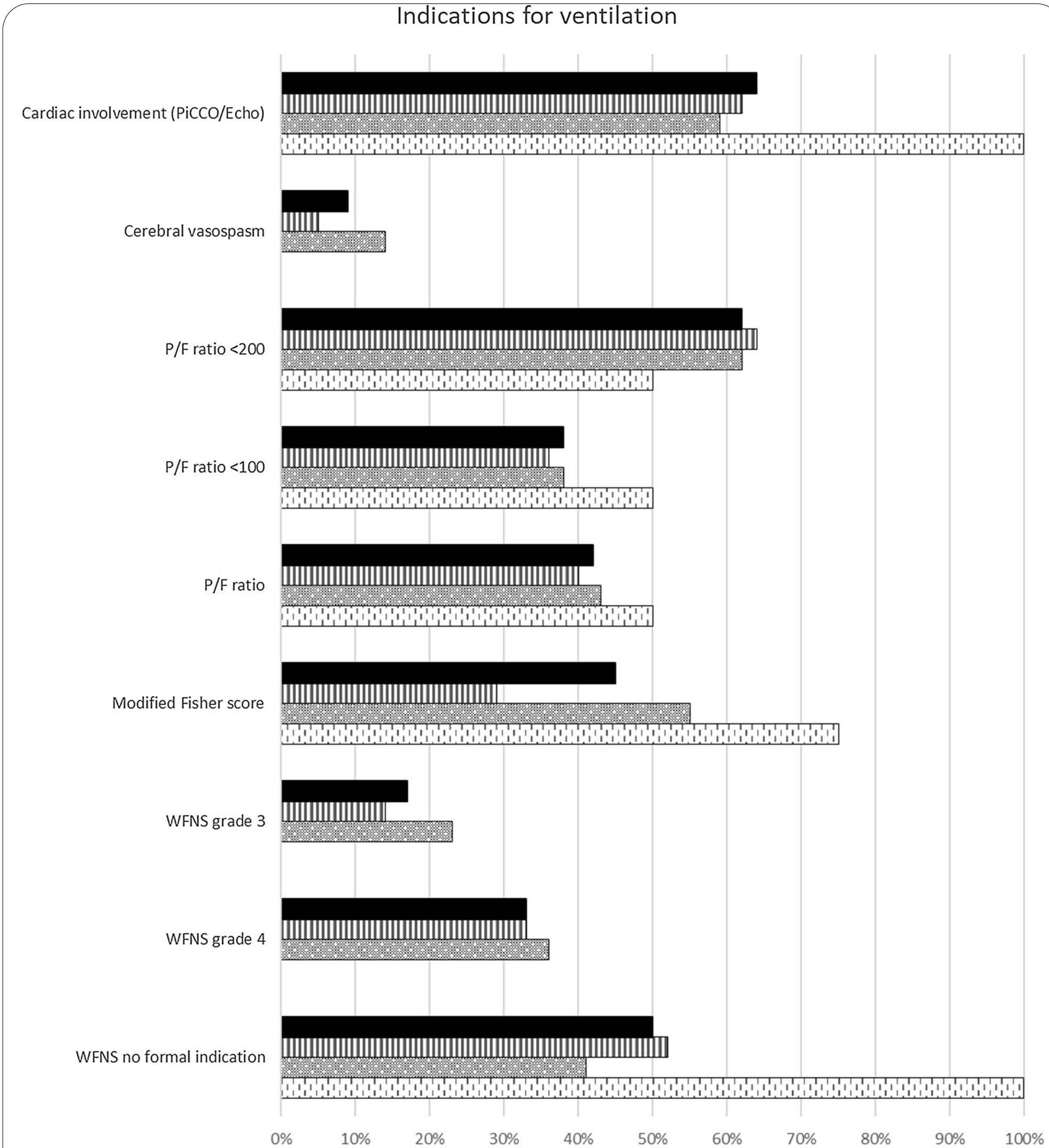
Most centers do not have strictly defined cutoff values to indicate ventilation in aSAH, as illustrated in Fig. 1. Nearly half of the centers answered that the modified Fisher score is a potential reason to indicate mechanical ventilation. More than half of the centers $n=26/45$ (58%) do not include the P/F ratio to objectify the level of pulmonary insufficiency. If the P/F ratio is used, more than one third of all centers tend to intubate relatively late (P/F ratio < 100 mmHg).

Normocapnia and normoxia are strived for by most reporting centers ($n=42/45$ (93%); $n=22/46$ (48%), respectively), but great variability was seen in their target paO_2, as opposed to a fair consensus regarding target $paCO_2$, as illustrated in Table 2.

No consensus was seen regarding tracheostomy: of $n=37/50$ (74%) reporting centers, $n=17/37$ (46%) perform late tracheostomies after 10 days, whereas $n=16/37$ (43%) perform them between days 3–10, and $n=4/37$ (11%) do so before day 3 ($p=0.064$).

Monitoring

With regards to monitoring, most centers rely on the Richmond agitation and sedation scale (RASS) $n=30/42$ (71%) and intracranial pressure (ICP) values $n=24/42$ (57%) to assess sedation levels. Invasive ICP monitoring is performed by either an intraparenchymal ICP probe $n=35/44$ (79%) and/or external ventricular drainage $n=39/44$ (89%). Most centers also manage blood pressure in accordance to cerebral perfusion pressure (CPP) $n=37/41$ (90%), but heterogeneity was observed in CPP target values both within and between the groups, as illustrated in Table 3. The use of advanced hemodynamic monitoring by means of pulse contour cardiac output (PiCCO) was mainly reported by UH $n=8/20$ (40%) and



	WFNS no formal indication	WFNS grade 4	WFNS grade 3	Modified Fisher score	P/F ratio	P/F ratio <100	P/F ratio <200	Cerebral vasospasm	Cardiac involvement (PiCCO/Echo)
■ Total	50%	33%	17%	45%	42%	38%	62%	9%	64%
◫ UH	52%	33%	14%	29%	40%	36%	64%	5%	62%
▩ HVC	41%	36%	23%	55%	43%	38%	62%	14%	59%
□ LVC	100%	0%	0%	75%	50%	50%	50%	0%	100%

Fig. 1 Indications for ventilation in the interrogated centers. All participating institutions were asked if WFNS grade, modified Fisher score, *P/F* ratio, cerebral vasospasm or cardiac involvement, as determined by PiCCO or echocardiography, were indications for ventilation. *HVC* high-volume centers, *LVC* low-volume centers, *UH* university hospitals

Table 2 Target partial pressure of oxygen and carbon dioxide, as reported by centers

Center	Target paO_2			Target $paCO_2$		
	80–100 mmHg	> 100 mmHg	Depending on SaO2	< 35 mmHg	35–45 mmHg	> 45 mmHg
Total	22	16	8	1	42	2
UH	11	5	4	1	19	0
HVC	9	8	1	0	15	2
LVC	2	3	3	0	8	0

HVC high-volume centers, *LVC* low-volume centers, *UH* university hospitals

Table 3 Use of cerebral perfusion pressure monitoring in the centers and target values

Center	CPP monitoring					
	Yes					No
	> 60 mmHg	> 70 mmHg	> 80 mmHg	> 90 mmHg	Individual	
All	12	12	5	5	3	5
UH	6	3	2	4	2	3
HVC	4	5	3	0	1	1
LVC	2	4	0	1	0	1

HVC high-volume centers, *LVC* low-volume centers, *UH* university hospitals

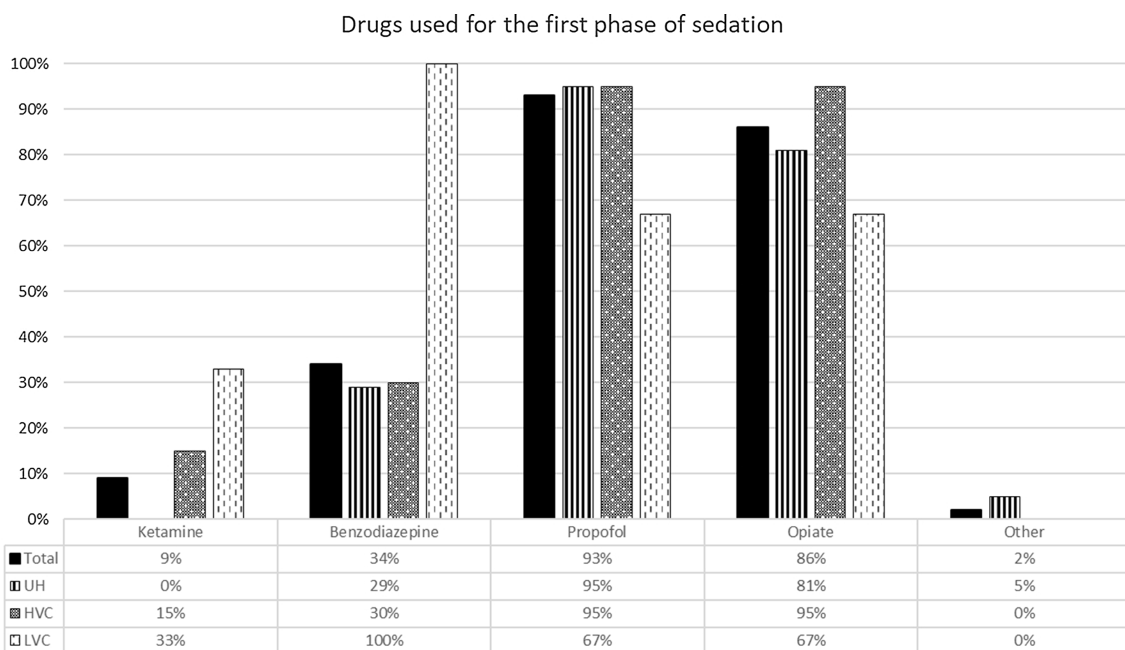
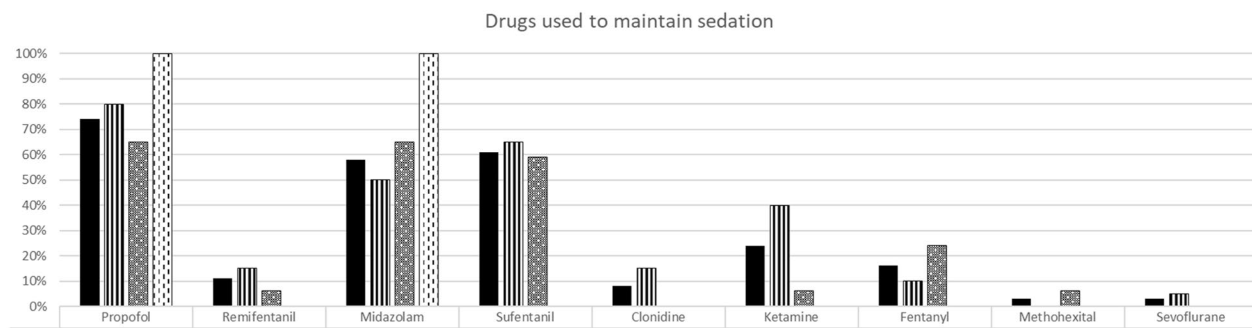


Fig. 2 Drugs used for the first phase of sedation in the interrogated centers, stratified by center type. While great variability was observed, most centers appear to use a combination of propofol and opiates to induce sedation in aSAH patients. *HVC* high-volume centers, *LVC* low-volume centers, *UH* university hospitals

HVC $n = 8/20$ (40%). Brain tissue oxygen ($PtiO_2$) was reported exclusively in UH $n = 10/20$ (50%) and HVC $n = 3/20$ (15%).

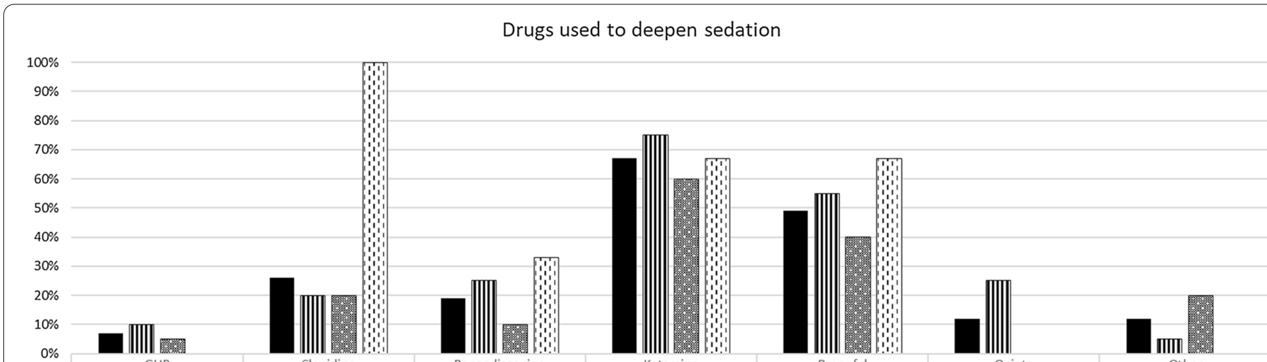
Sedation Management

Most centers $n = 46/50$ (92%) reported on the amount of aSAH patients undergoing VST: in $n = 21/46$ (46%) of centers, > 50% of their aSAH patients undergo VST. Most institutions $n=44/50$ (88%) reported on the drugs used for the first phase of sedation therapy. As illustrated in Fig. 2, heterogeneity was seen both within and between UH, HVC and LVC. While propofol appears to be used by the majority $n=41/44$ (93%), it is variably combined with opiates, benzodiazepines and ketamine. First-line sedative for the maintenance of sedation was reported by $n=38/50$ (74%) of the participating institutions; here, great variability was seen both within and between UH, HVC and LVC. Only one UH $n=1/38$ (3%) reported on the use of volatile sedatives for the maintenance of sedation (Fig. 3). There appears to be no consensus with regards to the type of drug employed to deepen sedation level among the $n=43/50$ (84%) reporting institutions (Fig. 4). UH and HVC reported the use of barbiturates more frequently than LVC to deepen sedation level ($p=.297$). Most institutions reporting on the maximum number of sedatives used $n=33/43$ (77%) routinely employ three or more medications, with no statistically significant difference between UH, HVC and LVC ($p=0.851$). The drug dosages used for sedation are also largely variable, as illustrated by two examples in Fig. 5.



	Propofol	Remifentanil	Midazolam	Sufentanil	Clonidine	Ketamine	Fentanyl	Methohexital	Sevoflurane
Total	74%	11%	58%	61%	8%	24%	16%	3%	3%
UH	80%	15%	50%	65%	15%	40%	10%	0%	5%
HVC	65%	6%	65%	59%	0%	6%	24%	6%	0%
LVC	100%	0%	100%	0%	0%	0%	0%	0%	0%

Fig. 3 Drugs used for the maintenance of sedation in the interrogated centers, stratified by center type. While great variability was observed, most centers appear to use a combination of propofol, midazolam and sufentanil to maintain sedation in aSAH patients. Only one UH employs inhalational anesthetics to maintain sedation in this patient population. *HVC* high-volume centers, *LVC* low-volume centers, *UH* university hospitals



	GHB	Clonidine	Benzodiazepine	Ketamine	Propofol	Opiate	Other
Total	7%	26%	19%	67%	49%	12%	12%
UH	10%	20%	25%	75%	55%	25%	5%
HVC	5%	20%	10%	60%	40%	0%	20%
LVC	0%	100%	33%	67%	67%	0%	0%

Fig. 4 Drugs used to deepen sedation level in the interrogated centers, stratified by center type. Ketamine appears to be the most commonly employed drug in all center types for this purpose. *HVC* high-volume centers, *LVC* low-volume centers, *UH* university hospitals

Discussion

While evidence-based guidelines for aneurysm occlusion and the detection and prevention of DCI in the setting of aSAH have been published [2, 4], NCC of this patient population is less well standardized. As summarized in

(See figure on next page.)

Fig. 5 Variability of the maximum dosages of midazolam and sufentanil. Maximum dosages of midazolam vary by a factor of 8.5 (smallest "maximum" dosage = 7 mg/h, largest "maximum" dosage = 60 mg/h), while maximum dosages of the opioid sufentanil vary by a factor of 62.5 (smallest "maximum" dosage = 40 μg/h, largest "maximum" dosage > 2500 μg/h

Table 3, most guidelines fail to make specific recommendations regarding NCC management of aSAH patients. The Neurocritical Care Society attempted to overcome this gap by issuing a multidisciplinary consensus conference (NCCSMCC) in 2011 [3]. Here, management of DCI and systemic complications were addressed, but an essential part of NCC, VST, was completely left unmentioned. Almost half of aSAH patients undergo VST, as evinced in our survey, making this a formidable gap in patient care. In this study, we found great heterogeneity in all aspects analyzed, possibly reflecting this lack of guidelines and/or published expert consensus.

Ventilation and Indications for Tracheostomy

Evidence regarding ventilation therapy in aSAH patients is practically non-existant; there are German national guidelines for invasive ventilation [6], but they do not consider the particular challenges of ventilation in the aSAH population. The guidelines of the Brain Trauma Foundation also comment on ventilation therapy, but for patients with severe TBI [10]. Both guidelines might be partially adoptable for indicating, adjusting and steering ventilation in aSAH patients, but they were not issued taking into consideration the specific needs of this population.

In TBI, prior guidelines recommended hyperventilation as a temporizing measure for the reduction of elevated ICP. However, the most recent guidelines for TBI issued by The Brain Trauma Foundation have revised this notion and currently advocate for normoventilation. Some survey respondents reported target hyperventilation. This practice is particularly concerning given that hyperventilation has been shown to exacerbate DCI in cases of aSAH due to additional vasoconstriction [11, 12], thus rendering the extrapolation of now outdated TBI guidelines for aSAH potentially dangerous. Additionally, most centers reported a narrow corridor for their target $paCO_2$ between 35 and 45 mmHg. However, recent evidence has exhibited potential benefits of controlled hypercapnia in patients with aSAH, for $paCO_2 > 60$ mmHg has been shown to increase cerebral blood flow (CBF) and thus possibly prevent DCI [13]. Therefore, consideration of patient-tailored $paCO_2$/CBF is important.

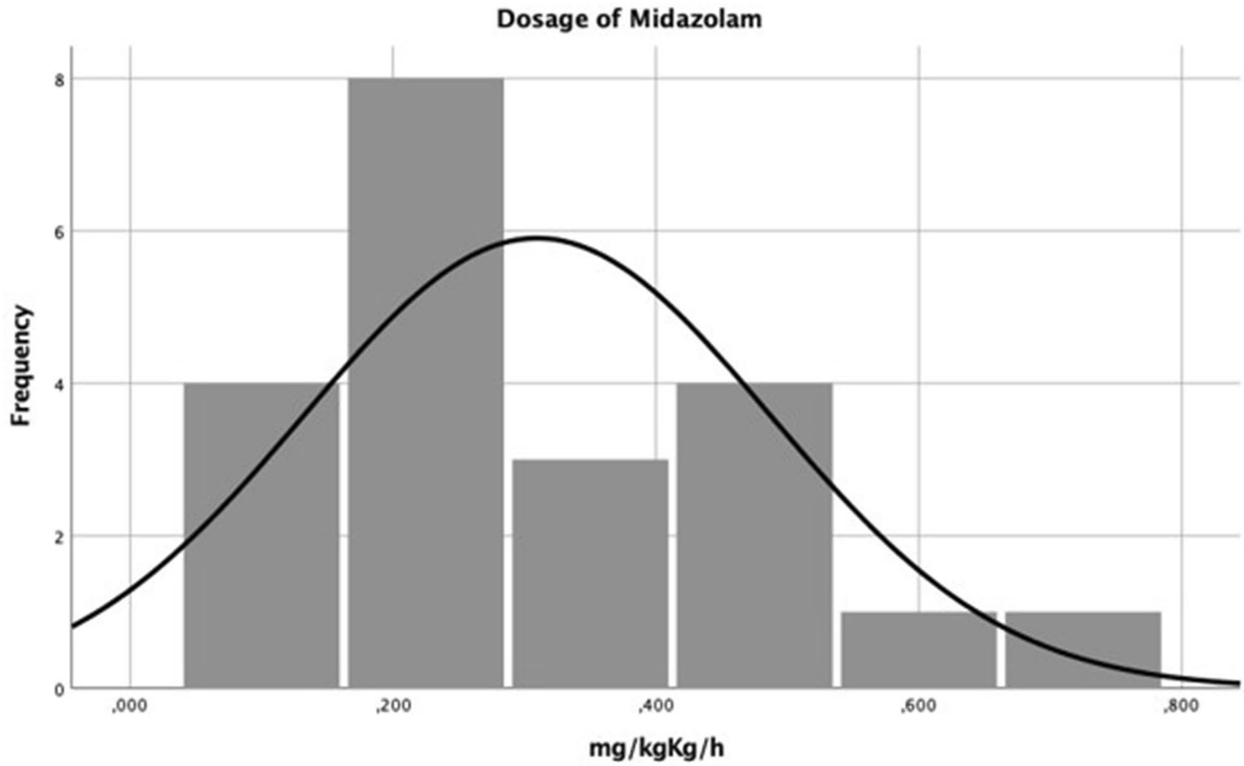
Regarding tracheostomy, no consensus in its indication was observed among the reporting centers. A recent meta-analysis [14] on early versus late tracheostomy in patients with early brain injury (EBI) suggested reductions in mortality and ICU length of stay favoring early tracheostomy. On the other hand, the SETPOINT trial [15], conducted on 60 patients with different forms of severe stroke, showed reduced use of sedatives and ICU mortality favoring early tracheostomy. However, this study was not powered to assess these secondary endpoints, and its successor SETPOINT2 [16] is still underway. A subgroup analysis of aSAH patients enrolled in SETPOINT2 might yield higher quality evidence pertaining to the optimal timepoint for tracheostomy in aSAH. However, no controlled trials have assessed the optimal timing of tracheotomy in aSAH patients, and guidelines fail to address this point as well, thus providing an explanation for the heterogeneity in the answers received in our survey.

Monitoring

In accordance with the International Multidisciplinary Consensus Conference on Multimodality Monitoring (IMCCMM) [13], most centers perform ICP monitoring, either by an intraparenchymal probe and/or EVD. Additionally, most surveyed centers employ RASS to monitor sedation level in their aSAH patients. RASS is the only diagnostic tool to evaluate both sedation level and agitation/delirium that has been validated for NCC patients and that has been shown to provide reliable information when assessing aSAH patients [17].

Multimodality monitoring was almost exclusively used by UH and HVC. On the one hand, both the American Heart Association (AHA) guidelines for the management of aSAH [2] and the Neurocritical Care Society consensus [3] recommend advanced hemodynamic monitoring using thermodilution methods in unstable aSAH patients. On the other hand, monitoring cerebral oxygenation in high-grade aSAH patients can provide valuable information and warn of impending DCI and/or infarction [18]. Additionally, IMCCMM [13] recommends the use of multimodality monitoring in poor-grade aSAH. Failure to adhere to these recommendations and to employ these adjuncts in LVC might have a detrimental effect on patient outcome and should be critically evaluated on a national level to ensure patient safety.

Another striking finding in our survey was the great heterogeneity in CPP targets reported by centers. While CPP-oriented therapy has proven to be efficient in TBI, with guidelines recommending CPP maintenance between 60 and 70 mmHg [10], recent studies have


Dosage of Midazolam
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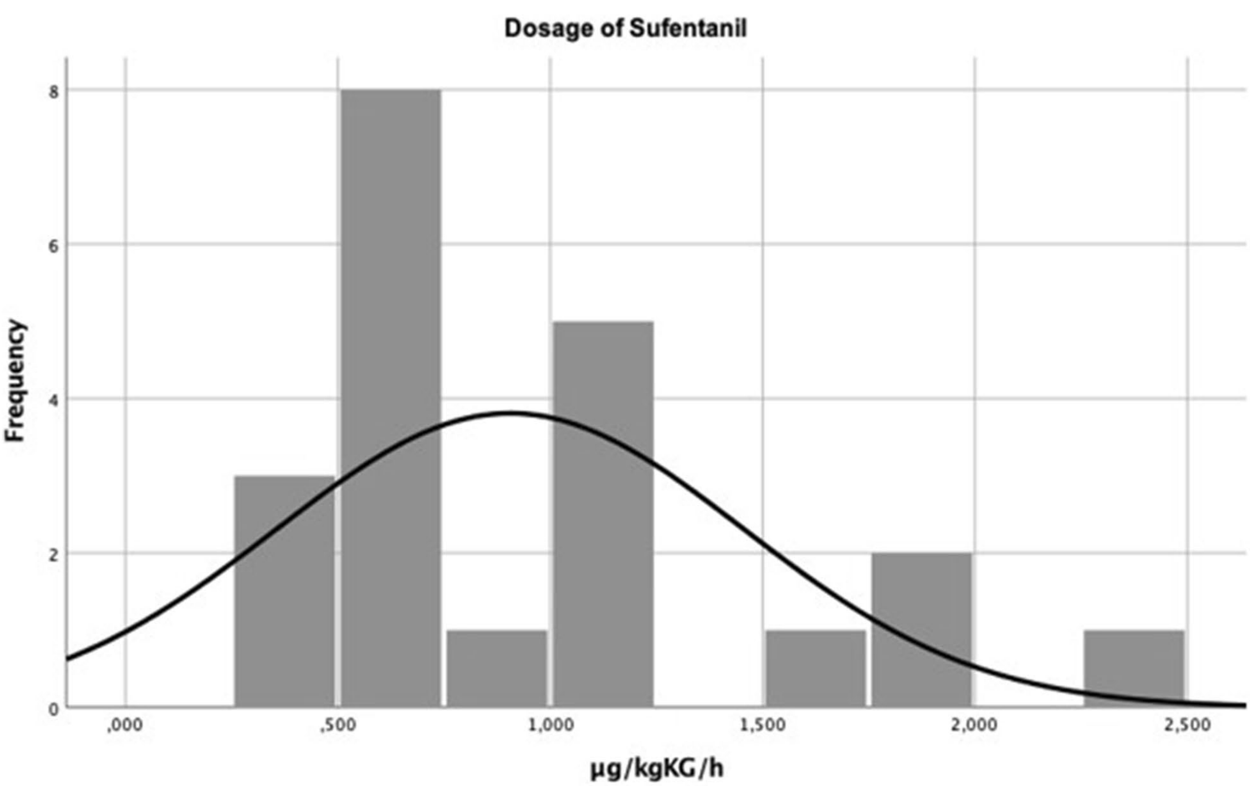
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emphasized the importance of targeting the optimal CPP (CPPopt) for each patient based on their unique autoregulation, as estimated by the pressure reactivity index (PRx) [19]. In the setting of poor-grade aSAH, CPP values below 70 mmHg have been associated with poor functional recovery and brain tissue hypoxia [20], but CPPopt is also emerging as a potentially useful tool in the diagnosis and treatment of DCI [21]. Evidently, further studies are needed to guide CPP management in aSAH, and further recommendations in this regard should be incorporated into national and international guidelines.

Sedation

Our survey revealed great heterogeneity in the choice of medications used for sedation irrespective of center caseload, but we were able to identify some commonalities. Firstly, propofol was the most commonly used drug for the first phase of sedation therapy and maintenance in surveyed centers. This drug has become an extremely popular sedative in NCC, as it has a rapid onset and a short duration of action, thus allowing for "daily sedation interruption" (DSI) and regular neurological examinations.

Similarly, midazolam was one of the most commonly used drugs to maintain sedation. This GABAergic drug has an established role in the management of IHTN in TBI [10], which could possibly explain its use in the aSAH patient population as an extrapolation of the TBI experience. The use of both these drugs has been commented on in the most current guidelines for TBI [10], but the evidence behind them does not suffice for the investigators to make a recommendation on them. In our national guidelines for VST [6], both drugs are regarded with equipoise, but the administration of propofol is recommended over midazolam in case of desired prompt neurological evaluation.

Another drug commonly used for sedation maintenance in our survey was sufentanil. One could hypothesize that both propofol and sufentanil are popular due to their short duration of action and the ability to perform DSI, which is also mentioned as one of their advantages in our national guidelines [6]. However, in a meta-analysis evaluating sedation protocols versus DSI, no statistically significant differences were observed regarding patient outcome [22].

Sedation Deepening

When interrogated on sedation deepening, most UH und HVC reported the use of ketamine. German national guidelines [6] comment amply about the use of ketamine in patients with TBI and IHTN; most of their recommendations are classified as "could do", and do not have a binding character. Nonetheless, there is emerging data in the literature advocating for the use of ketamine in aSAH [23, 24], as it has been associated with a lower incidence of DCI-related infarctions and lower ICP in aSAH patients. Interestingly, LVC resort to clonidine for the deepening of sedation. This drug fails to find mention in national guidelines and the evidence supporting its use in the ICU is very scarce [25].

Another interesting finding of our survey regarding sedation deepening was the establishment of barbiturate coma in UH and HVC, but not in LVC. TBI guidelines recommend sedation deepening with these drugs for refractory IHTN [10]. In aSAH, barbiturates have been shown to reduce refractory symptomatic vasospasm [26], underscoring their potential role in the management of aSAH beyond ICP control.

Similarly, only one UH reported the use of inhalational anesthetics as first-line therapy to maintain sedation, and the use of volatile sedation was more common in UH than in HVC/LVC. Guidelines fail to mention the use of inhalational anesthetics in aSAH or NCC, and this form of anesthesia can be considered experimental in this setting, as there are only smaller studies evaluating it in aSAH to date [27, 28].

In sum, our survey revealed that most UH and HVC manage sedation in similar fashion, incorporating more recent evidence pertaining to the specific pharmacological effects of different drugs in aSAH. On the contrary, LVC adhere to general guidelines and extrapolate TBI ones in their drug selection.

Future Directions

Based on the results obtained, we have identified several questions that, in our opinion, merit the development of randomized-controlled trials and/or expert consensus guidelines to both homogenize and improve patient treatment in this devastating condition:

- Optimal sedatives in the setting of aSAH, pertaining not only to ICP and cerebral metabolism control, but also to the reduction of DCI and poor patient outcome.
- Ventilator settings and goals of ventilation therapy in aSAH.
- Timing of tracheostomy in aSAH patients.

Limitations

Results obtained from a voluntary survey should be interpreted with caution. One of the main drawbacks of a survey is its susceptibility to both selection and recall biases, as it relies on self-report and cannot be controlled for its accuracy. In our study in particular, survey answers might have been skewed one way or another depending on the subspecialty of the reporting colleague (intensivist vs neurosurgeon vs neurologist), thus reflecting their personal preferences with regards to drug selection for sedation and preferred ventilator parameters, and not their institutional average at large. Furthermore, colleagues might have interpreted questions differently and understood "sedation induction"/"first phase of sedation" and "sedation deepening" in differing ways, for instance.

The overall response rate to our survey was high, at nearly 50%. Based on their reported treatment volume and the incidence of aSAH in Germany, we calculated the representativeness of our results to be at 63% of the treatment volume of aSAH in Germany. While these figures appear high, a subset of questions was answered only by some of the participating centers, thus lowering the overall generalizability of our results. The length of our survey, with 70 questions, might have been a deterring factor influencing survey completion.

Another aspect that might limit generalizability of our results is differing treatment protocols and available medications in other countries: different benzodiazepines and opioids might be used in other parts of the world with greater predilection than in Germany.

Conclusions

Our study demonstrates that attitudes and practices pertaining to NCC in aSAH are heterogeneous, possibly reflecting the lack of good quality evidence and differing interpretations thereof. We observed some extrapolation of TBI guidelines for the management of aSAH, such as thresholds for ventilation and target CPP in some centers, but the pathophysiology of both entities is completely different. Failing that, expert consensus statements would greatly contribute to guiding NCC of aSAH.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-020-01029-8) contains supplementary material, which is available to authorized users.

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SH-D: Data analysis, manuscript conception and writing; CS: Data collection and figure creation; JS: Study design; OM: Data analysis, manuscript redaction; VR: Study design, manuscript redaction; DM: Manuscript redaction; CB: Study conception, data anaylsis, study design, manuscript conception and writing.

Conflict of interest

The authors declare that they have no conflicts of interest.

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