Sonographic Monitoring of Midline Shift Predicts Outcome after Intracerebral Hemorrhage

Ines C. Kipthuth Hagen B. Huttner Lorenz Breuer Stefan Schwab
Martin Köhrmann

Department of Neurology, Universitätsklinikum Erlangen, Erlangen, Germany

Key Words

Intracerebral hemorrhage · Midline shift · Transcranial duplex sonography

Abstract

Background: Spontaneous intracerebral hemorrhage (ICH) and the evolution of subsequent perihemorrhagic edema lead to midline shift (MLS), which can be assessed by transcranial duplex sonography (TDS). In this observational study, we monitored MLS with TDS in patients with supratentorial ICH up to day 14 after the ictus, and then correlated MLS with the outcome 6 months after hospital discharge. **Methods:** Sixty-eight patients with spontaneous ICH (volume >20 cm³) were admitted during a 1-year period between April 2009 and April 2010. Sixty-one patients fulfilled the inclusion criteria and were eligible for analysis. TDS to measure MLS was performed upon admission and then subsequently, using serial examinations in 24-hour intervals up to day 14. Statistical tests were used to determine cut-off values for functional outcome and mortality after 6 months. **Results:** The median National Institutes of Health Stroke Scale (NIHSS) score upon admission was 21 and the mean hematoma volume was 52 cm³. NIHSS score, functional outcome, hematoma volume and MLS were correlated in the examined patient cohort. ICH score upon admission, hematoma volume and the extent of MLS on days 1–14 were predictive

of functional outcome and death. Values of MLS showed two peaks, the first between day 2 and day 5 and the second between day 12 and day 14, indicating that edema progresses not only during the acute but also during the subacute phase. Depending on the time point, an MLS of 4.5–7.5 mm or greater indicated an impending failure of conservative therapy. An MLS of 12 mm or greater at any time indicated mortality with a sensitivity of 69%, a specificity of 100% and positive and negative predictive values of 100 and 74%, respectively. **Conclusions:** MLS seems to be a crucial factor for outcome after ICH. Apart from the hematoma volume itself, edema adds to the intracranial pressure. To monitor MLS in early patient management after ICH, TDS is a useful noninvasive bedside alternative, avoiding increased radiation exposure and repeated transportation of critically ill patients. Cut-off values may help to reliably predict functional outcome and treatment failure in patients undergoing maximal neurointensive therapy.

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Introduction

Spontaneous intracerebral hemorrhage (ICH) often leads to severe disability or death [1]. An early estimation of prognosis and the monitoring of treatment are essential in order to be able to inform patients and their

families and for decision-making regarding further treatment. Clinical outcome in patients with ICH varies, depending on a number of parameters, e.g. baseline hematoma volume, ventricular involvement, evolution of perihemorrhagic edema, age and blood glucose level [2–5]. In addition, midline shift (MLS) is a known prognostic factor for unfavorable outcome after ICH [6]. In clinical practice, repeated cranial computed tomography (CT) is often used to monitor MLS, causing increased radiation exposure and requiring repeated transportation of critically ill patients, which is associated with increased morbidity and mortality [7–9]. Transcranial duplex sonography (TDS) offers a noninvasive bedside alternative to radiologic methods. TDS measurements are valid for diagnosing and monitoring various neurological diseases including ICH [10–13]. In addition, TDS monitoring of the early dynamics of MLS reliably predicts early mortality and outcome in conservatively treated hemispheric ischemic stroke [14]. In contrast to ischemic stroke, MLS in ICH constitutes both the hematoma volume itself and the edema formation, which may make the prediction of outcomes more difficult. The objective of this study was to evaluate TDS as a monitoring method of MLS in patients with ICH who underwent maximal conservative treatment in the first 2 weeks after the ictus. Measurements were then correlated with mortality and functional outcome 6 months after hospital discharge. Cut-off values of MLS that best predicted mortality and outcome were calculated.

Materials and Methods

Patients and ICH Management

This study was performed in a specialized neurological intensive care unit at a tertiary university hospital (Erlangen, Germany). Patients with ICH (volume $>20 \text{ cm}^3$) who were admitted between April 2009 and April 2010 were eligible. Exclusion criteria were an insufficient temporal bone window, hematoma evacuation and do-not-treat/resuscitate (DNT/DNR) orders at any time during the hospital stay. Patients who received DNT/DNR orders were excluded because the aim of this study was to predict functional outcome in patients with maximal neurointensive therapy and detect the MLS values that differentiate between survival and death in this patient cohort. ICH management was performed according to European recommendations [15]. Patients with intraventricular hemorrhage received extraventricular drainages according to institutional protocol and the discretion of the treating neurointensive care physician. Hematoma volume was calculated from CT imaging using the formula of ellipsoids $[(\text{length} \times \text{width} \times \text{height})/2]$, as previously described [16]. Hematoma growth was defined as an increase of $\geq 33\%$ of the parenchymal hematoma volume compared to baseline [17].

Outcome Assessment

Functional outcome was assessed using the modified Rankin scale (mRS) at 6 months. The mRS was evaluated by a certified rater using a semistructured telephone interview with the patients or with their closest relatives [18]. Given that only ICHs with a volume $>20 \text{ cm}^3$ were included in the study, functional outcomes were classified into favorable (mRS 0–2), acceptable (mRS 3–4) and unfavorable (mRS 5–6) outcomes. The cut-off point between acceptable and unfavorable outcomes was chosen according to the results of studies evaluating the opinions of the patients and their relatives on acceptable outcomes in a comparable intensive-care patient cohort [19, 20].

Standard Protocol Approval, Registration and Patient Consent

Consent to participate in this study was obtained from all patients or their relatives/legal guardians. The study was approved by the local ethics committee.

Neurosonographic Methods

A single experienced examiner [I.C.K., trained in sonographic imaging of the intracranial ventricles by M.K., who is an ultrasound instructor of the highest level for the DEGUM (German Society for Ultrasound in Medicine) for 6 months before this study was initiated] performed TDS examinations with a phased-array ultrasound system equipped with a 1.33 MHz transducer (SIEMENS Acuson Antares) through the contralateral temporal bone window, as described before [14]. The probe was tilted approximately 10° upward to scan axially with a penetration of 100–140 mm and a dynamic range of 22 dB to visualize the contralateral skull bone. Contrast, image brightness and time-gain compensation were adjusted to receive the best image. The third ventricle was visualized at a depth of 60–80 mm and was identified by its parallel hyperechogenic margins and the surrounding hypoechogenic thalami [13]. The distance between the contralateral calotte and the margins of the third ventricle were measured in perpendicular lines bilaterally (fig. 1). The deviation from the presumed midline was measured by the equation $(A - B)/2$ (fig. 1). TDS was performed at the time of admission and in 24 ± 3 -hour intervals for 14 days or until death or discharge.

Statistics

Statistical tests were two-sided, and the significance level was set at $\alpha = 0.05$. The distribution of the data was assessed with the Kolmogorov-Smirnov test. Continuous and categorical variables are expressed as means and SDs, medians and ranges or percentages, as appropriate. Patients were grouped according to outcome and their age, sex, medical history, length of ventilation, National Institutes of Health Stroke Scale (NIHSS) score, mRS, hematoma volume and MLS were compared. Correlations between parameters and prediction of functional outcome using stepwise forward inclusion logistic regression models and receiver operating characteristic (ROC) analyses were calculated. All parameters that reached significance or at least showed a trend in univariate analyses were included in the multivariate analyses. For each time point of sonographic MLS measurement, a separate model was calculated. Analyses were conducted with the SPSS 17.0 software package (SPSS Inc., Chicago, Ill., USA).

Fig. 1. Schematic illustration of MLS evaluated by TDS: insonation through the respective contralateral temporal bone window. Distances from the right (a) and left (b) tabulae of the skull to the third ventricle (V3). h = Hematoma; td = transducer.

Table 1. Demographic and clinical data of all patients and in each functional outcome group after 6 months

Characteristics	All (n = 61)	mRS ≤2 (n = 5)	mRS ≤4 (n = 20)	mRS = 6 (n = 30)
Age, years	71 (60–79)	64 (61–65)	66 (60–77)	74 (60–81)
Gender, female	23 (37.8)	2 (40.0)	8 (40.0)	12 (40.0)
Arterial hypertension	35 (57.4)	3 (60.0)	11 (55.0)	19 (63.3)
Hyperlipidemia	39 (63.9)	4 (80.0)	13 (65.0)	20 (66.7)
Diabetes mellitus	14 (22.9)	1 (20.0)	5 (25.0)	7 (23.3)
LOV, days	11 (6–21)	10 (8–16)	17 (10–24)	7 (3–16)
NIHSS at admission	21 ± 11	7 ± 6	15 ± 11	26 ± 11
Hematoma volume, cm ³	51.9 ± 36.1	24.8 ± 8.6	27.1 ± 9.0	76.1 ± 38.2
Hematoma localization (right)	34 (55.7)	3 (60.0)	11 (55.0)	19 (63.3)
Ventricular involvement	42 (68.9)	2 (40.0)	10 (50.0)	24 (80.0)

Values are median (IQR), number (%) or mean ± SD. LOV = Length of ventilation.

Results

Patients and Baseline Characteristics

Within a 1-year period, 68 patients with an ICH volume of >20 cm³ were screened. Sixty-one of them fulfilled the inclusion criteria and provided consent to participate in this study (1 female patient provided insufficient temporal bone windows, 2 patients underwent hematoma evacuation and 4 had DNT/DNR status). The median NIHSS score upon admission was 21 and the mean hematoma volume was 52 cm³. The demographic and clinical data of the

patients are given in table 1. The parameters of baseline NIHSS score, mRS at 6 months after discharge, hematoma volume and MLS were correlated with one another in the examined patient cohort ($-0.3 > r > 0.3$; $p < 0.05$).

Cut-Off Values of MLS for Impending Treatment Failure and Mortality

Table 2 gives the results of ROC analyses (specificity and sensitivity) and positive and negative predictive values (PPV and NPV) for critical values of MLS for each day (days 1–14), indicating death after 6 months. These data

Fig. 2. MLS of each patient depending on time (days 1–14) and mortality [survival (white) vs. death (black)]. Cut-off values derived from ROC analyses that best predict mortality are drawn as horizontal lines at all time points.

Table 2. Critical MLS derived from the ROC analyses: specificity, sensitivity, PPV and NPV of MLS for mortality after 6 months

Day	MLS, mm	Sensitivity	Specificity	AUC	PPV	NPV	n	p
1	>4.5	0.714	0.828	0.874	83.3	77.4	61	<0.001
2	>6.5	0.786	0.897	0.910	89.7	81.3	61	<0.001
3	>6.5	0.786	0.897	0.900	87.5	86.2	60	<0.001
4	>7.5	0.786	0.966	0.916	93.3	87.1	54	<0.001
5	>6.5	0.857	0.897	0.937	84.4	82.8	53	<0.001
6	>5.5	0.857	0.862	0.919	84.8	85.7	51	<0.001
7	>5.5	0.714	0.862	0.897	80.6	76.7	49	<0.001
8	>5.5	0.643	0.828	0.869	81.3	79.3	49	<0.001
9	>5.5	0.714	0.828	0.837	81.3	76.7	48	<0.001
10	>5.5	0.786	0.828	0.866	84.4	82.1	48	<0.001
11	>6.5	0.857	0.931	0.897	87.1	83.3	47	<0.001
12	>6.5	0.857	0.966	0.908	90.3	86.7	44	<0.001
13	>5.5	0.786	0.966	0.894	90.0	84.4	43	<0.001
14	>4.5	0.857	0.862	0.898	82.4	82.8	41	<0.001

The second column gives the critical MLS (cut-off value) for the respective day after the ictus. The subsequent columns give the results of the ROC analyses of the critical MLS cut-off values. n = Number of patients included in the respective analysis.

indicate that there was a cut-off value ranging between 4.5 and 7.5 mm (depending on the day) that differentiated between survival and death in patients who underwent conservative therapy (fig. 2). These values show two peaks, the first between day 2 and day 5 and the second on days 12–14, indicating that in ICH, edema growth progresses not only during the acute phase but also during

the subacute phase. This is particularly distinctive in patients who did not survive the 6-month period after the ictus (fig. 3). An MLS of more than 12 mm at any given time indicated mortality with a sensitivity of 69%, a specificity of 100%, a PPV of 100% and an NPV of 74%. The area under the curve (AUC) was 0.957.

Prediction of Outcome and Mortality

To test the relevance of sonographic MLS measurements at different time points, logistic regression models correcting for relevant factors identified in univariate analysis were calculated. Results are given in table 3. Beside MLS at various time points, these analyses showed that ICH score on admission, ICH volume and absence of early hematoma growth were predictive of functional outcome. NIHSS score at admission showed a trend towards an association with outcome after 6 months, and ventricular extension of hemorrhage revealed a trend towards an association with unfavorable outcome and death.

Detection of Early Hematoma Growth and Rapid Increase of Edema

In 14 patients, an increase of MLS of 5 mm or more within 24 h was observed (median 6 mm; IQR 5–6 mm). Upon follow-up CT, 3 of these patients (21%) had hematoma growth $\geq 33\%$ compared to the previous CT. No other patients exhibited hematoma growth during the study period. The sensitivity of this end point reached 100%, but both the specificity and PPV for rebleeding were low. However, all 14 patients with an MLS increase >5 mm within 24 h had an unfavorable outcome, and only 1 survived the first 6 months (mRS = 5).

Discussion

Even though transcranial sonography, particularly the sonographic identification of midline structures, was among the first medical ultrasound applications [21], the advancement of other imaging modalities has since limited its use. This is mainly due to the typical drawbacks of TDS, which include examiner dependency, susceptibility to an insufficient temporal bone window, lower spatial resolution and possible artifacts. However, while these drawbacks may impede the use of TDS in certain clinical applications, the advantages of the method, including its bedside availability and the lack of radiation exposure, make TDS an ideal tool for other clinical situations that require frequent control examinations. The study did not aim to replace follow-up radiological examinations in this patient population, but to test whether daily serial TDS can serve as a complementary bedside screening method to identify individual patients with impending failure of maximal conservative neurointensive care treatment.

Detection and monitoring of MLS can easily be accomplished by TDS. Earlier studies revealed a high cor-

Fig. 3. ROC curve for worst MLS of each individual patient and mortality after 6 months. An MLS of 12 mm or greater indicated mortality with a sensitivity of 69%, a specificity of 100% and a PPV and NPV of 100 and 74%, respectively. The AUC was 0.957.

relation of the determination of the third ventricle between TDS and CT and a robust inter- and intraobserver reliability [22, 23]. In addition to the monitoring of MLS, serial TDS examinations allow the assessment of lateral ventricular width, ventricular involvement of the ICH, monitoring of posthemorrhagic hydrocephalus and detection of early hematoma growth [11–13, 24].

MLS seems to be one of the most crucial factors for functional outcome after ICH [6]. Apart from the hematoma itself, vasogenic and cytotoxic brain edema add to the intracranial rise in volume, leading to increased intracranial pressure, tissue shift and, in severe cases, subsequent cerebral herniation. To identify patients at risk, early predictors of elevated intracranial pressure, such as incipient MLS, need to be included in the decision-making process. This can be accomplished by repeated CT scans or, more conveniently, by repeated bedside TDS. Tang et al. [13] observed a correlation among ICH volume, short-term functional outcome and MLS measured by TDS. This has been confirmed by Fogelholm et al. [25], who reported a correlation between MLS and mortality at 28 days. In our study, repeated TDS exhibited high correlations between MLS and functional status after 6 months. In contrast to the ICH score on admission, which

Fig. 4. Box-plot of MLS on days 1–14 in patients who died within 6 months after ICH. Two peaks of MLS are found. The circles (days 1 and 14) indicate statistical outliers.

Table 3. Stepwise logistic regression models calculated for MLS on each day until day 14 depending on functional outcome after 6 months

	mRS ≤2 (n = 5)			mRS ≤4 (n = 20)			mRS = 6 (n = 30)		
	exp (coef)	95% CI	p value	exp (coef)	95% CI	p value	exp (coef)	95% CI	p value
MLS day 1	0.43	0.17–1.02	0.06	0.69	0.54–0.88	<0.05	1.53	1.21–1.97	<0.05
MLS day 2	0.39	0.16–0.94	<0.05	0.59	0.44–0.79	<0.05	1.88	1.37–2.59	<0.05
MLS day 3	0.24	0.06–0.99	<0.05	0.61	0.46–0.80	<0.05	1.97	1.38–2.47	<0.05
MLS day 4	0.30	0.08–1.19	0.09	0.64	0.50–0.82	<0.05	2.90	1.31–6.03	<0.05
MLS day 5	0.12	0.02–1.04	0.06	0.59	0.43–0.80	<0.05	2.69	1.31–5.51	<0.05
MLS day 6	0.17	0.02–1.28	0.09	0.58	0.43–0.79	<0.05	2.41	1.35–4.21	<0.05
MLS day 7	0.13	0.02–1.18	0.07	0.54	0.38–0.76	<0.05	2.21	1.41–3.49	<0.05
MLS day 8	0.17	0.02–1.31	0.09	0.53	0.37–0.75	<0.05	1.87	1.30–2.78	<0.05
MLS day 9	0.19	0.03–1.20	0.08	0.53	0.37–0.75	<0.05	1.63	1.26–2.18	<0.05
MLS day 10	0.13	0.01–1.22	0.07	0.54	0.38–0.76	<0.05	2.01	1.32–2.97	<0.05
MLS day 11	n/a	n/a	n/a	0.56	0.41–0.77	<0.05	2.36	1.41–3.77	<0.05
MLS day 12	n/a	n/a	n/a	0.58	0.44–0.78	<0.05	4.24	1.23–14.61	<0.05
MLS day 13	n/a	n/a	n/a	0.52	0.36–0.75	<0.05	3.45	1.40–8.45	<0.05
MLS day 14	n/a	n/a	n/a	0.49	0.32–0.74	<0.05	4.24	1.36–13.18	<0.05

The model corrected for age, sex, NIHSS at admission, pre-ICH mRS, ICH score, ICH volume, localization of ICH, ventricular hemorrhage and early hematoma growth. Significant parameters are expressed in bold. CI = Confidence interval; n/a = not available.

also predicted long-term outcome, the advantage of such repeated measurements is that they allow for the identification of a clinical course for each specific patient instead of giving a statistical prognosis based on a single finding upon admission.

MLS differed significantly as early as day 1 between those patients who survived and those who died during the study period (table 2; fig. 2). Furthermore, ROC analyses defined a cut-off value for MLS ranging between 4.5 and 7.5 mm, depending on the time point after ICH, above which the chances for survival drastically decreased. As all enrolled patients received maximal con-

servative but not surgical therapy, such as hematoma evacuation, these may be the cut-off values that indicate the impending failure of conservative strategies.

An MLS above 12 mm at any time during the clinical course had a PPV of 100% for a fatal outcome at 6 months. Data on MLS for the prediction of functional outcome in patients with ICH are sparse compared to patients with ischemic stroke. However, a number of publications report that increasing MLS negatively correlates with survival. However, most of the existing publications either correlate any MLS, regardless of its extent, to functional outcome [6], or correlate any MLS above 5 mm to mortal-

ity [25, 26]. Only one study, albeit one examining a cohort of ischemic stroke patients, defines specific critical values of MLS at several time points until 40 h after the ictus [14].

The critical MLS cut-off values that best predicted mortality after 6 months show two peaks indicating progressing edema growth not only during the acute phase but also during the subacute phase (fig. 4). This finding is supported by previously published data [27–29] and may also be explained by the observation that the first time point corresponds to the early phase of initial edema formation and the titration phase of treatment, while the second peak coincides with the usual phase for tapering antiedematous medication.

Previous studies using serial TDS examination to directly visualize the hematoma at early time points have shown that TDS can be used to reliably detect early hematoma growth [12]. In contrast, by measuring the increase of MLS within 24 h, our method can only indirectly address this question by evaluating the dynamics of MLS evolution. A cut-off MLS increase of >5 mm over 24 h identifies patients with rebleeding with a sensitivity of 100%, although its specificity and PPV remain low. Thus, further CT scanning is indicated in this subgroup as defined by TDS and will identify all patients with early hematoma enlargement. In addition, even in the absence of rebleeding, such a rapid and dynamic increase of MLS defines a subgroup of patients with grim prognosis and no patient in this group can be expected to achieve an acceptable outcome.

It needs to be highlighted that all patients in this study received maximal conservative neurointensive therapy, including endovascular normothermia and antiedematous drugs, throughout the trial. Without these therapy strategies, lower MLS values might have been fatal. As previous studies have indicated that DNT/DNR orders themselves may be the reason for a grave prognosis [30, 31], we felt that the inclusion of these patients (n = 4) might result in a change in cut-off MLS value and thus possibly lead to a reduction in neurological therapy in some patients with borderline MLS values who would otherwise have been treated differently. We therefore stress that the data in this study should not lead to the deprivation of neurointensive therapy in patients with increased MLS who are not undergoing maximal treatment.

There are limitations to our study, mainly involving the small patient number and the single-center design. However, with its focus on daily TDS examinations over the first 14 days, the study still includes 770 TDS exami-

nations. Correlations of TDS with CT results and the inter- and intraobserver reliabilities of TDS were not assessed in our study because these aspects were evaluated in previous trials [32]. A recurrent limitation of TDS is an insufficient temporal bone window, which may be encountered especially in older female patients [33]; however, we only excluded 1 female patient on these grounds. Compared to other applications of TDS, identifying the prominent echogenic mid-line (3rd ventricle) is far less dependent on insonation windows. This is also illustrated by the fact that this application was feasible more than 50 years ago using much less sophisticated techniques [34, 35].

Conclusion

Our data suggest that serial TDS examinations of MLS may be used to monitor intensive-care treatment and to predict functional outcome and mortality in patients with supratentorial ICH. The method does not aim to replace standard diagnostics (e.g. follow-up CT scans) but offers a complementary noninvasive bedside screening method, which enables the treating physician to identify patients with impending failure of maximal intensive-care management. However, as this study was single-centered and based on a relatively small number of patients, further studies to confirm the data are required.

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