Aus der Klinik und Poliklinik für Neurochirurgie

der Universitätsmedizin Rostock

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Epileptischer Anfall und Status epilepticus bei Patienten mit Subduralhämatomen

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Gott, meiner Frau und meiner Familie gewidmet

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1. Einleitung

Epileptische Krampfanfälle sind eine der häufigsten Komplikationen bei einem Schädel-Hirn Trauma (SHT) mit einer Inzidenz von 1,5 bei milden bis zu 17,0 bei schweren SHT [1]. Nach dem ersten Anfallsereignis ist das Risiko für Entwicklung einer Epilepsie im Verlauf von bis zu 10 Jahren erhöht, kumulativ beträgt das Risiko 86% innerhalb von 2 Jahren [2]. Als Folge des epileptischen Anfalls wird eine progressive Neurodegeneration in Gang gesetzt, die zu neurologischen und psychosozialen Veränderungen und einer erhöhten Mortalität führen [3]. Als Risikofaktoren für die Entwicklung von epileptischen Anfällen im SHT bestehen verschiedene Parameter, insbesondere das Subduralhämatom (SDH) [1,4,5].

Das SDH ist definitionsgemäß eine Blutung in den normalerweise nicht vorhandenen Raum zwischen Dura mater und Arachnoidea. Ursächlich hierfür sind Verletzungen des Kortex und der ihn begleitenden Gefäße, meist kortikale Venen (seltenerweise auch Arterien), die als sogenannte Brückenvene vom Kortex über den Mittelspalt zum Sinus sagittalis superior ziehen. Das SDH hat aufgrund der hohen Inzidenz und der Schwere des Krankheitsbildes, welches häufig zu einer Schwerbehinderung und damit zu großen gesundheitlichen und gesellschaftlichen Kosten führt, eine enorme Bedeutung im klinischen Alltag [6,7]. Das SDH kann man je nach Auftreten vom zeitlichen Intervall und Ätiologie zwischen akuten, subakuten und chronischen SDH unterscheiden. Das akute SDH (aSDH) entwickelt sich nach einem SHT, welche häufig mit Coup und Contrecoup-Verletzungen sowie Scherverletzungen (e.g. diffuse axonale Schädigung) von kortikalen und subkortikalen Substanzen vergesellschaftet ist. Im Gegensatz dazu entsteht das chronische SDH (cSDH) durch ein mildes SHT oder Bagatelltrauma. Infolgedessen wird eine Inflammation mit einer Angiogenese und Fibrinolyse in Gang gesetzt, welche zur Entwicklung von äußeren und inneren Membranen führen. Die äußere Membran beinhaltet fragile fenestrierte Kapillaren, wodurch eine kontinuierliche Leckage des Blutes entsteht. Mit einer aktivierten Fibrinolyse bleibt das Hämatom flüssig. Zudem kommt es zur Flüssigkeitsexsudation in den subduralen Raum durch den osmotischen Gradient, wodurch das cSDH größer wird [8]. Daher ist die Differenzierung nach Typ des SDHs bedeutend, weil sich erstens die therapeutische Maßnahme und Prognose und zweitens die zugrundeliegenden pathophysiologischen Mechanismen und Risiken für die Entwicklung epileptischer Anfälle unterscheiden.

Als Vorarbeit haben wir ein systematisches Review über epileptische Anfälle bei SDH von 1961 bis 2016 nach der *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Leitlinie durchgeführt und folgende Aussagen treffen können [9]: Erstens gibt es zwischen aSDH und cSDH einen deutlichen Unterschied bezüglich der Prävalenz und Risikofaktoren des epileptischen Anfalles. Zweitens gibt es nur begrenzte Daten zu epileptischen Anfällen und Status epilepticus bei aSDH. Drittens herrscht in der Literatur eine große Diskrepanz über epileptische Anfälle bei cSDH aufgrund der Heterogenität der analysierten Parameter sowie einer fehlenden Unterscheidung zwischen akut symptomatischen und späten epileptischen Anfällen. Dies hatte zur Folge, dass eine Meta-Analyse nicht möglich war und keine zusammenfassende Aussage getroffen werden konnte.

In der aktuellen Leitlinie der *Brain Trauma Foundation* gibt es seit der Arbeit von Temkin et al. im Jahr 1990 nur wenig Veränderung [10,11]. Eine prophylaktische antiepileptische Therapie kann bei einem schweren SHT für eine Woche eingesetzt werden, um die Rate an akut symptomatischen Anfällen zu reduzieren. Dies hat jedoch keinen Einfluss auf das Outcome (Evidenzklasse II) [11]. Problematisch wird die Lage durch die sogenannten nicht-konvulsiven Anfälle, die klinisch inapparent und nur über eine kontinuierliche Oberflächen-Elektroenzephalographie (EEG) als Anfalls- oder Statusmuster nachzuweisen sind. Diese subklinischen nicht-konvulsiven Anfälle sind von hoher Bedeutung, weil diese für die schlechte Prognose trotz erfolgreicher Operation und unauffälliger radiologischer Befunde verantwortlich sind [12].

Zusammengefasst kommt epileptischen Anfällen bei Patienten mit SDH ein besonderer Stellenwert zu, da diese therapie- und prognoseentscheidend sind. Ziel der Arbeiten ist es, der Frage nachzugehen, wie oft und mit welchen Risikofaktoren und Konsequenzen epileptische Anfälle, oder gar ein Status epilepticus, bei aSDH und cSDH in Erwachsenen und Kindern auftreten, um Hochrisikopatienten schneller zu erkennen und therapieren zu können. Des Weiteren soll ein neuer therapeutischer Ansatz in Behandlung von cSDH vorgestellt werden, um das Risiko eines epileptischen Anfalls zu reduzieren.

2. Fragestellung, Methodik und Ergebnisse der Originalarbeiten

Die vorliegende kumulative Habilitationsschrift fasst fünf Arbeiten zusammen, die sich mit epileptischen Anfällen und Status epilepticus bei akuten und chronischen SDH in erwachsenen und pädiatrischen Patienten beschäftigen. Ziel der Arbeiten ist es, der Frage nachzugehen, inwiefern epileptische Anfälle und Status epilepticus bei SDH eine klinische Relevanz haben und welche diagnostischen und therapeutischen Maßnahmen zu einer Optimierung der Behandlung führen kann.

Die Voraussetzung für eine einheitliche wissenschaftliche Analyse und praktische Anwendung im klinischen Alltag ist eine einfache und valide Volumenberechnung des SDHs (**OA 1**). Basierend auf dem Ergebnis der Validierungsstudie wurden die nachfolgenden Studien mit der gewählten Methodik untersucht.

In der zweiten Arbeit (**OA 2**) wurden epileptische Anfälle bei akuten SDH untersucht. Insbesondere wurde hier ein *Risiko-Score-System* für epileptische Anfälle entwickelt, um erstens Patienten mit hohem Risiko eines Anfalls zu identifizieren und zweitens den Einsatz einer prophylaktischen antiepileptischen Therapie zu spezifizieren. Die nachfolgende vergleichbare Studie (**OA 3**) konzentriert sich dann auf die seltenen Fälle von aSDH bei pädiatrischen Patienten.

In der vierten Arbeit (**OA 4**) beschäftigten wir uns mit epileptischen Anfällen und Status epilepticus bei chronischem SDH, wie häufig diese vorkommen, welche Risikofaktoren hierbei wichtig sind und ob die Anfälle eine Auswirkung auf das Outcome haben. Vor allem gilt das cSDH als eines der häufigsten Krankheitsbilder im klinischen Alltag eines Neurochirurgen. Der Fokus der aktuellen Forschung liegt auf der Reduktion von Rezidivhämatomen, welche ebenfalls einen Risikofaktor für einen epileptischen Anfall darstellen. Daher untersucht abschließend die letzte Arbeit (**OA 5**) eine neue therapeutische Möglichkeit, welche die Rezidivrate des cSDHs reduzieren soll, um das Risiko eines Anfalles ebenfalls zu reduzieren und die Prognose der Patienten zu verbessern. Alle Arbeiten wurden nach Erhalt eines zustimmenden Ethikvotums durchgeführt.

OA1. Genauigkeit der ABC/2 Volumenformel im Vergleich zur computergestützten volumetrischen Analyse von Subduralhämatomen

Won SY, Zagorcic A, Dubinski D, Quick-Weller J, Herrmann E, Seifert V, Konczalla J. Excellent accuracy of ABC/2 volume formula compared to computed-assisted volumetric analysis of subdural hematomas. *PLoS One. 2018 Jun 26;13(6):e0199809.*

Fragestellung: Die Indikation zur chirurgischen Behandlung des cSDHs wird nach der klinischen Symptomatik und dem Volumen des SDHs gestellt. Daher ist es im klinischen Alltag wichtig, eine einfache, valide Methode zur Volumenmessung des SDHs zu haben, um die Hämatomvolumina objektiviert vergleichen und therapeutische Entscheidungen schneller treffen zu können. Darüber hinaus kann eine einfache Volumenformel für die Durchführung und Analyse der Studien eine große Hilfestellung sein. Bereits zuvor beschäftigten sich mehrere Studien mit einer vereinfachten ellipsoiden Volumenformel, ABC/2, welche eine hohe Genauigkeit bei der Volumenmessung von intrazerebraler Blutung (ICB) und Epiduralhämatom (EDH) zeigte [13–15]. Da die geometrische Form des SDHs sich von einer ellipsoiden Form der ICB und des EDHs unterscheidet, haben wir die Hypothese aufgestellt, dass die ABC/2 Formel nicht für die Volumenmessung des SDHs geeignet ist. Ziel dieser Arbeit war die Volumina gemessen durch die ABC/2 Formel und computergestützte volumetrische Analyse zu vergleichen und gegebenenfalls eine neue klinisch einfach anwendbare Formel für die Volumenmessung des SDHs zu entwickeln.

Material und Methoden: In dieser Studie wurden 83 Patienten mit cSDH eingeschlossen, die zwischen 2016 und 2017 in der neurochirurgischen Abteilung behandelt wurden. Beidseitige Subduralhämatome wurden zweifach gezählt. Daraus resultierten insgesamt 100 SDH für die Analyse. Zur Messung der Hämatomvolumina wurde die präoperative CT-Bildgebung mit einer 5mm Schichtdicke benutzt. Die ABC/2 Formel wurde folgendermaßen angewendet: Die maximale Länge des SDHs von anterior nach posterior wurde als A (cm, eine maximale perpendikulare Linie zu A in der gleichen Schicht als B (cm) und die maximale Tiefe wurde als C (cm) definiert. Für die Tiefenmessung wurde die Schichtanzahl des gesichteten SDHs gezählt und mit der Schichtdicke (5 mm) multipliziert. Die Berechnung des Hämatomvolumens erfolgte durch die Multiplikation von AxBxC dividiert durch zwei. Die computergestützte volumetrische Messung erfolgte anhand Region-of-Interest Messung über die BrainLab Software (Fa. BrainLab, München). Die statistische Auswertung erfolgte mittels SPSS (IBM,

SPSS 22,0, Chicago, USA). Für die Korrelation der beiden volumetrische Methoden wurden Linear-Regressions- und Bland-Altman Regressionsanalyse verwendet. Als Signifikanzniveau wurde $\alpha \leq 0{,}05$ angenommen.

Ergebnisse: Das mittlere Volumen war 106,3±47,4cm^3 in der ABC/2 Messung im Vergleich zu 104,6±47,7cm^3 in der computergestützten Messung ohne einen signifikanten Unterschied. In der Linear-Regressionsanalyse konnte eine hochsignifikante Korrelation zwischen den beiden Methoden gezeigt werden (R^2=0,934, Steigung=0,975). Das Ergebnis konnte mittels Bland-Altman-Regressionsanalyse bestätigt werden (R^2=0,947, p<0,001). Des Weiteren wurde keine signifikante unerwünschte Abweichung (p=0,101) oder Trend (p=0,777) der beiden Methoden festgestellt.

Schlussfolgerung: Die ABC/2 Volumenformel zeigt eine exzellente Genauigkeit für die Bestimmung des SDH-Volumens vergleichbar zur computergestützten volumetrischen Analyse. Daher kann diese einfach verwendbare Formel für den klinischen Alltag sowie die Forschung unabhängig von der Größe des SDHs sicher benutzt werden.

OA2. Epileptische Anfälle bei Patienten mit chirurgischer Behandlung des akuten Subduralhämatoms – Inzidenz, Risikofaktoren, Outcome und Entwicklung eines neuen Score-Systems für prophylaktische antiepileptische Therapie (*Gate-24 score*)

Won SY, Dubinski D, Herrmann E, Cuca C, Strzelczyk A, Seifert V, Konczalla J, Freiman TM. Epileptic Seizures in Patients Following Surgical Treatment of Acute Subdural Hematoma-Incidence, Risk Factors, Patient Outcome, and Development of New Scoring System for Prophylactic Antiepileptic Treatment (*GATE-24 score*). *World Neurosurg. 2017 May;101:416-242*.

Fragestellung: Epileptische Anfälle sind häufige klinische Manifestation bei SDH und die Inzidenz bei aSDH beträgt zwischen 24-36% [16,17]. Die Prognose des aSDHs wird durch verschiedene Faktoren beeinflusst, jedoch gelten epileptische Anfälle als ein unabhängiger negativer prognostischer Faktor [17]. Daher ist es sehr wichtig, Patienten mit einem hohen Risiko für Entwicklung eines epileptischen Anfalls zeitnah zu identifizieren und therapieren. Ziel dieser Studie war, Risikofaktoren für epileptische Anfälle bei aSDH herauszufiltern, um damit ein *Risiko-Score-System* zu entwickeln.

Material und Methoden: Insgesamt wurden 139 Patienten mit aSDH von 2007 bis 2015 in die Studie eingeschlossen, die in der neurochirurgischen Abteilung behandelt wurden. Demographische Daten, klinische Parameter wie die *Glasgow Coma Scale* (GCS) bei Aufnahme und 24h postoperativ, Zeitpunkt der Operation, Antikoagulation und *Glasgow Outcome Scale* (GOS) bei Entlassung und 3 Monaten nach der Entlassung wurden untersucht. Als epileptischen Anfall wurden alle Ereignisse entsprechend der Definition der *International League Against Epilepsy* (ILAE) aus dem Jahre 2010 gewertet [18]. Die statistische Auswertung erfolgte mittels SPSS (IBM, SPSS 22,0, Chicago, USA). Risikofaktoren für epileptische Anfälle wurde mit einer univariaten und multivariaten logistischen Regressionsanalyse identifiziert. Die Gewichtung der einzelnen Parameter wurden für den *GATE 24-score* verwendet. Zusätzlich erfolgte eine ROC-Analyse und Bestimmung des Cut-off-Wertes mittels Youden Index. Als Signifikanzniveau wurde $\alpha \leq 0{,}05$ angenommen, bei multivariaten Analysen $\alpha \leq 0{,}1$.

Ergebnisse: Von 139 Patienten in der Studie eingeschlossenen Patienten hatten 53 Patienten (38,1%) einen epileptischen Anfall. 21 von 53 Patienten (39,6%) hatten einen präoperativen,

34 von 53 Patienten (64,2%) einen postoperativen sowie 2 Patienten (3,8%) einen prä- und postoperativen epileptischen Anfall. In der univariaten Analyse wurden GCS≤8 bei Aufnahme, GCS ≤ 8 24h nach der Operation, Breite des aSDH ≥ 1,4cm und Antikoagulation als Risikofaktoren identifiziert. Der Zeitpunkt der Operation >24h nach der Aufnahme wies sich als zusätzlicher Risikofaktor in der Subgruppenanalyse mit der Unterteilung in prä- und postoperativen Anfälle. In der multivariaten Analyse zeigten sich GCS 24h nach der Operation, Zeitpunkt der Operation und Antikoagulation als unabhängige signifikante Risikofaktoren. Basierend auf diesen Ergebnissen wurde der *GATE 24-score* entwickelt mit einem Cut-off-Wert von 24 Punkten und einer AUC von der ROC-Analyse von 0,71 (95% Cl 0,62-0,80). Der *GATE 24-score* war folgendermaßen definiert: **G**CS 24h nach der Operation: 3-15 Punkte, keine **A**ntikoagulation: 5 Punkte, Zeitpunkt („**T**iming“) der Operation <24h: 5 Punkte, **E**pileptische Therapie nicht notwendig bei ≥**24** Punkten. Die Sensitivität des *GATE 24-score-Systems* lag bei 59,3% und die Spezifität bei 73,6%. Patienten mit einem epileptischen Anfall hatten bei Entlassung ein signifikant schlechteres Outcome (GOS 1-3) im Vergleich zu den Patienten ohne epileptische Anfälle (84,9% vs. 58,2%; p<0,001). Ein ähnliches Ergebnis zeigte sich in 3 Monaten nach der Entlassung (72,1% vs. 43,1%; p=0,003). Die allgemeine Mortalitätsrate innerhalb von 3 Monaten betrug 30,6%. Ebenfalls war die Mortalitätsrate bei Patienten mit epileptischen Anfällen, im Vergleich zu denen ohne Anfälle, signifikant erhöht (41,9% vs. 23,1%; p=0,05).

Schlussfolgerung: Die epileptischen Anfälle sind entscheidend für die Prognose der Patienten mit einem aSDH. Das *GATE 24-score-System* ist der erste Schritt für die Identifizierung der Hochrisikopatienten für einen epileptischen Anfall und könnte für die selektionierte Anwendung einer prophylaktischen antiepileptischen Therapie in Erwägung gezogen werden.

OA3. Klinische Relevanz des epileptischen Anfalls bei pädiatrischen Patienten mit isoliertem akuten Subduralhämatom ohne Schädigung des Hirnparenchyms

Won SY, Dubinski D, Behmanesh B, Strzelczyk A, Seifert V, Konczalla J, Freiman TM. Clinical Relevance of Seizure in Pediatric Patients with Isolated Acute Subdural Hematoma without Parenchymal Brain Injury. *J Neurol Surg A. 2019 Jul;80(4):233-239.*

Fragestellung: In der vorherigen Arbeit konnten wir zeigen, dass der epileptische Anfall eine häufige Komplikation bei aSDH darstellt und einen großen Einfluss auf das Outcome der Patienten hat. Der Fokus der vergangenen Studie lag bei erwachsenen Patienten, jedoch wurde bereits in der Literatur beschrieben, dass das Auftreten von Anfällen bei SHT in pädiatrischen Patienten dreimal so häufig ist wie im Vergleich zu Erwachsenen [19,20]. Daher war das Ziel der Arbeit, die Inzidenz, Risikofaktoren und Outcome bei pädiatrischen Patienten mit aSDH und epileptischen Anfällen zu untersuchen.

Material und Methoden: Patienten unter 18 Jahren mit einem isolierten aSDH, die zwischen 2007 und 2016 in der neuropädiatrischen Abteilung behandelt worden sind, wurden in die Studie eingeschlossen. Die klinischen Daten wurden analysiert und das Outcome bei Entlassung, sowie 3 Monaten nach der Entlassung, anhand *King´s Outcome Scale for Childhood Head Injury* (KOSCHI) bestimmt (1: Tod, 2: Vegetativer Status, 3: Schwere Behinderung, 4: Mittelgradige Behinderung, 5: Leichte Behinderung). Als gutes Outcome wurde ein KOSCHI von 4-5 definiert. Die statistische Auswertung erfolgte mittels GraphPad Prism (6,0, Graphpad Software Inc., La Jolla, California, USA). Die Daten zwischen den beiden Gruppen wurden mit Mann-Whitney-U-Test und Fisher-Exact-Test verglichen. Als Signifikanzniveau wurde $\alpha \leq 0{,}05$ angenommen.

Ergebnisse: Insgesamt wurden 10 pädiatrische Patienten mit einem isolierten aSDH in die Studie eingeschlossen. Hiervon waren 4 Patienten weniger als einen Monat alt, 4 Patienten zwischen einem Monat und einem Jahr, 1 Patient zwischen 1 bis 2 Jahre und ein weiterer Patient über 2 Jahre alt. Das aSDH bei den Patienten unter einem Monat war ausschließlich durch eine Komplikation bei Geburt bedingt. Bei den übrigen Patienten waren es Traumata, Misshandlungen oder eine unklare Ätiologie. Die Anfallsrate bei pädiatrischen Patienten betrug 60%. Davon hatten 3 Patienten einen präoperativen, 2 Patienten einen postoperativen Anfall und 1 Patient prä- sowie postoperative epileptische Anfälle. Die höchste Inzidenz eines

epileptischen Anfalls hatten die Patienten unter einem Monat (75%), davon entwickelten 67% eine späte Epilepsie. Als Risikofaktoren für einen epileptischen Anfall wurden niedriger pädiatrischer GCS (pGCS) bei Entlassung ($p=0,03$), niedriger pGCS 24h nach der Operation ($p=0,03$) und Grad der Mittellinienverlagerung ($p=0,02$) festgestellt. In 3 Monaten Verlaufskontrolle hatten alle pädiatrischen Patienten ohne epileptischen Anfall ein gutes Outcome (100%). Im Gegensatz dazu erlangte nur die Hälfte (50%) der Patienten mit einem epileptischen Anfall ein gutes Outcome. Eine Signifikanz konnte jedoch aufgrund der geringen Zahl der Patienten nicht erreicht werden ($p>0,05$).

Schlussfolgerung: Die Inzidenz eines epileptischen Anfalls bei pädiatrischen Patienten mit einem aSDH beträgt 60%, bei Kindern unter einem Monat sogar noch höher. Als Risikofaktoren wurden ein niedriger pGCS postoperativ und bei Entlassung, sowie Grad der Mittellinienverlagerung festgestellt. Aufgrund der niedrigeren Schwelle zwischen epileptiformer Entladung und klinischer Manifestation eines Anfalls, gerade im Vergleich zu den Erwachsenen, ist es daher empfehlenswert eine regelmäßige EEG Untersuchung auch bei milden Trauma durchzuführen und eine zeitnahe antiepileptische Therapie bei Hochrisikopatienten zu initiieren.

OA4. Epileptische Anfälle und Status epilepticus bei chronischen Subduralhämatomen

Won SY, Dubinski, Sautter L, Hattingen E, Seifert V, Rosenow F, Freiman TM, Strzelczyk A, Konczalla J. Seizure and status epilepticus in chronic subdural hematoma. *Acta Neurol Scand. 2019 Sep;140(3):194-203.*

Fragestellung: Die Inzidenz des epileptischen Anfalls bei cSDH variiert zwischen 2 und 42% [9]. Es wurden bereits mehrere Risikofaktoren für einen epileptischen Anfall bei cSDH beschrieben. Jedoch war eine Meta-Analyse bislang nicht möglich, weil die meisten Studien erstens keine Differenzierung zwischen akuten symptomatischen und späten epileptischen Anfällen und zweitens zu heterogene Parameter in den jeweiligen Studien untersucht hatten. Hinzu kommt noch die geringe Anzahl der Patienten, die in den jeweiligen Studien eingeschlossen waren, so dass hier kein einheitlicher Konsens ausgesprochen werden konnte. Daher war das Ziel dieser Arbeit, die Inzidenz der epileptischen Anfälle und Status epilepticus zu ermitteln und die Risikofaktoren mit den zuvor berichteten Parametern in einer großen Kohorte zu untersuchen sowie das Outcome der Patienten zu analysieren.

Material und Methoden: Im Rahmen einer retrospektiven Studie wurden Patienten in die Studie eingeschlossen, die zwischen 2010 und 2017 mit einem cSDH in der neurochirurgischen Abteilung behandelt wurden. Patienten mit begleitender parenchymaler Verletzung oder Kontusionen, intrazerebraler Blutung oder subarachnoidaler Blutung sowie der Vorgeschichte einer Epilepsie wurden ausgeschlossen. Neben den klinischen Daten wurden alle Parameter in die Analyse eingeschlossen, welche wir bereits zuvor im Rahmen eines systematischen Reviews über Anfälle bei SDH zusammengefasst hatten [9]. Nach der Leitlinie von ILAE wurde ein akuter symptomatischer Anfall (ASz) folgendermaßen definiert: Klinische Manifestation eines Anfalls oder Nachweis von iktalen EEG-Mustern innerhalb einer Woche nach der initialen Diagnose eines cSDHs. Ein Status epilepticus (SE) wurde definiert entweder als ein generalisierter tonisch klonischer Anfall, der mehr als 5 Minuten dauert, oder als ein komplexer fokaler Anfall, der mehr als 10 Minuten dauert [18]. Das Outcome wurde anhand des *modified Rankin Scale* (mRS) bei Entlassung und 3 Monaten nach der Entlassung bestimmt. Als gutes Outcome wurde ein mRS von 0-2 und als schlechtes Outcome ein mRS von 3-6 definiert. Die statistische Auswertung erfolgte mit dem Programm SPSS (IBM, SPSS 22,0, Chicago, USA). Univariate- und multivariate lineare Regressionsanalysen wurden durchgeführt, um die unabhängigen Risikofaktoren für ASz und SE zu eruieren. Für die

parametrischen Werte wurde t-Test und die nicht-parametrischen Werte Fisher-Exact-Test oder Chi-Quadrat-Test verwendet. Zusätzlich wurden die Odds Ratio mit 95% Konfidenzintervall kalkuliert. Als Signifikanzniveau wurde $\alpha \leq 0{,}05$ angenommen.

Ergebnisse: Insgesamt wurden 375 Patienten in die Studie eingeschlossen. Das mediane Alter betrug 75 Jahre [Interquartilsabstand 67,4-81,9] und 264 Patienten (70,3%) hatten ein unilaterales cSDH. Eine operative Entlastung der Blutung erfolgte in über 90% der Fälle, die restlichen Patienten wurden konservativ behandelt. Ein Rezidivhämatom trat bei 49 Patienten (13,1%) innerhalb von 14 Tagen und bei 60 Patienten (16%) innerhalb von 3 Monaten nach der Entlassung auf. Die Inzidenz von ASz/SE lag bei 17,1% (64 von 375 Patienten). Davon war 15,2% ASz und 1,9% SE. In der univariaten Analyse wurden folgende Risikofaktoren identifiziert: GCS ≤ 13 bei Aufnahme, Zustand nach Schlaganfall und Rezidivhämatom innerhalb von 14 Tagen. Die subdurale Drainage zeigte sich als ein protektiver Faktor. In der multivariaten Analyse blieben GCS ≤ 13 bei Aufnahme, Zustand nach Schlaganfall und Rezidivhämatom innerhalb von 14 Tagen als unabhängige Risikofaktoren für ASz/SE übrig. Ein gutes Outcome bei Entlassung konnte bei 254 Patienten (67,7%) festgestellt werden. Die Patienten mit ASz/SE hatten ein signifikant schlechteres Outcome bei Entlassung sowie 3 Monate nach der Entlassung ($p<0{,}001$). In der Subgruppenanalyse mit Unterteilung in ASz und SE hatten alle Patienten (100%) mit SE ein signifikant schlechteres Outcome bei Entlassung sowie 3 Monaten nach der Entlassung ($p<0{,}001$). Die Mortalitätsrate bei Patienten mit SE war 4,4-fach höher als im Vergleich zu den Patienten mit ASz und 7,1-fach höher als im Vergleich zu den Patienten ohne einen epileptischen Anfall.

Schlussfolgerung: ASz und SE sind häufige klinische Manifestation bei cSDH mit einer Inzidenz von 15% und 2%. Als Risikofaktoren wurden niedriger GCS bei Aufnahme, Zustand nach Schlaganfall und Rezidivhämatom identifiziert. Die Patienten mit ASz und SE haben ein schlechteres Outcome und eine hohe Mortalitätsrate. Daher sollte aus neurochirurgischer Sicht vor allem der Fokus auf die Reduktion des Rezidivhämatoms liegen. Des Weiteren sollte bei Patienten mit einem cSDH eine regelmäßige EEG-Untersuchung zur frühen Detektion des ASz und SE in Erwägung gezogen werden.

OA5. Angeleitetes Valsalva Manöver nach Bohrlochentlastung des chronischen Subduralhämatoms: Eine prospektive Kohortenstudie

Won SY, Dubinski D, Behmanesh B, Bernstock JD, Keil F, Freiman TM, Konczalla J, Seifert V, Gessler F. Supervised Valsalva Maneuver after Burr Hole Evacuation of Chronic Subdural Hematomas: A Prospective Cohort Study. *J Neurotrauma. 2020 Apr 1;38(7):911-917 14.*

Fragestellung: Das cSDH ist eine häufige Erkrankung mit zunehmender Inzidenz aufgrund der demographischen Entwicklung unserer Gesellschaft. Die Rezidivrate eines cSDHs wird zwischen 5-30% berichtet und der Fokus der vielen Forschungen liegt bei der Reduktion von Rezidivraten [21]. Vor kurzem hat Edlmann et al. insgesamt 26 randomisierte kontrollierte laufende Studien über die medikamentöse Behandlung mit Steroiden, Tranexamsäuren, verschiedene chirurgische Techniken sowie endovaskuläre Versorgung des cSDHs berichtet [22]. Jedoch gibt es bislang kaum eine Studie mit Fokus auf das postoperative Management, welches ebenfalls einen Einfluss auf die Rezidivrate haben kann. Das Ziel dieser Arbeit war es zu untersuchen, ob ein neues postoperatives Management in Form eines angeleiteten Valsalva Manövers (SVM) einen positiven Einfluss auf die Rezidivrate und Outcome eines cSDHs hat.

Material und Methoden: Die Studie wurde in *clinicaltrial.gov* registriert (NCT04060186). Im Rahmen einer prospektiven Kohortenstudie wurden alle Patienten mit cSDH eingeschlossen, die zwischen 2016 und 2019 in der neurochirurgischen Abteilung behandelt wurden. Patienten mit akutem/subakutem SDH, ohne einliegender Drainage oder postoperativem GCS <15 wurden von der Studie ausgeschlossen, um den Selektionsbias zu minimieren. Nach der Bohrlochentlastung des cSDHs und Einlage einer subduralen Drainage wurden die Patienten je nach Station in zwei Gruppen aufgeteilt: SVM- und Kontrollgruppe. Die Patienten in der SVM-Gruppe erhielten einen an einer Spritze angebrachten Handschuh, in den sie mindestens zweimal pro Stunde für 12 Stunden in den nächsten zwei Tagen aufgefordert waren, einen Luftstoß zu tätigen, bis der Handschuh eine maximale Spannung erreicht hatte. Eine postoperative CT Bildgebung wurde nach Entfernung der subduralen Drainage zwischen dem postoperativen Tag 1-3 durchgeführt und klinisch sowie radiologisch für mindestens 3 Monaten kontrolliert. Des Weiteren wurde das Outcome mittels *modified Rankin Scale* (mRS) bei Entlassung sowie 3 Monaten nach der Entlassung untersucht. Der primäre Endpunkt war die Rezidivrate zwischen den beiden Gruppen. Der sekundäre Endpunkt war die Morbidität sowie das Outcome der Patienten bei Entlassung und in 3 Monaten. Die statistische

Auswertung erfolgte mittels SPSS (IBM, SPSS 22,0, Chicago, USA). Für kategorische Parameter wurde ein Chi-Quadrat-Test verwendet. Die numerischen Daten wurden mit einem Median- und einem Interquartilabstand kalkuliert. Die Normalverteilung wurde mit Kolmogorow-Smirnow-Test überprüft. Im Fall einer Normalverteilung wurde ein t-Test verwendet, andernfalls ein Mann-Whitney-U-Test. Zusätzlich wurde eine logistische Regressionsanalyse durchgeführt, um unabhängige Parameter für den Einfluss auf die Rezidivrate und das Outcome zu untersuchen. Als Signifikanzniveau wurde $\alpha \leq 0{,}05$ angenommen.

Ergebnisse: Insgesamt wurden 176 Patienten mit einem cSDH eingeschlossen. Davon waren 94 Patienten im Interventionsarm und 82 Patienten im Kontrollarm. Klinische sowie radiologische Parameter waren zwischen den beiden Gruppen gut ausgeglichen. Die Rezidivrate innerhalb von 3 Monaten nach der Entlassung war signifikant niedriger in der SVM-Gruppe im Vergleich zu der Kontrollgruppe (17% vs. 29,3%; p=0,05). In der Regressionsanalyse zeigte sich das SVM als der einzige unabhängige Faktor für die Reduktion der Rezidivrate. Hinzu kommt, dass die Infektionsrate (hpts. Pneumonie) signifikant niedriger in der SVM-Gruppe war im Vergleich zu der Kontrollgruppe (1,1% vs. 13,4%; p<0,001). Komplikationen wie Synkope oder hämodynamische Instabilität trat bei keinem Patienten der SVM-Gruppe auf. Bei Entlassung hatten 137 Patienten (77,8%) ein gutes Outcome. Die Patienten in der SVM-Gruppe hatten signifikant besseres Outcome im Vergleich zu der Kontrollgruppe (p=0,004). Nach 3 Monaten war das Ergebnis ebenfalls unverändert (p=0,008).

Schlussfolgerung: SVM ist eine sichere und effektive Methode, um die Rezidivrate des cSDHs zu reduzieren und zugleich die Infektionsrate zu senken. Diese Methode ist einfach in jeder Abteilung umsetzbar und kann das Outcome der Patienten durch den positiven Effekt verbessern.

3. Diskussion

Die Diagnose eines epileptischen Anfalls oder Status epilepticus wird durch die klinische Manifestation oder epileptische Anfallsmuster in der EEG-Untersuchung gestellt. Problematisch sind die nicht-konvulsiven Anfälle oder der Status epilepticus, welche zu einer verzögerten Diagnostik und Therapieeinleitung führen [12]. Vespa et al. konnte im Rahmen einer kontinuierlichen EEG-Monitoring bei Patienten mit SHT zeigen, dass mehr als 50% der epileptischen Anfälle nicht-konvulsiven Charakters waren [23]. Des Weiteren haben vergangene Studien gezeigt, dass bei Patienten mit SDH häufig epileptiforme Abnormalitäten wie zum Beispiel die periodische lateralisierte epileptiforme Entladung auftreten, welche durch periodisches Auftreten von spitzen- und scharfen Wellen in 1-3 Sekundenintervallen charakterisiert sind [5,24,25]. Dieses können Signale für ein Kontinuum zwischen iktalem und interiktalem Status sein, welcher als Biomarker für einen subklinischen Anfall gilt [5]. Rudzinski et al. berichtete eine hohe Inzidenz der EEG-Abnormalitäten von 87% bei Patienten mit aSDH. Diese Studien geben uns einen Hinweis, dass wahrscheinlich die Inzidenz des epileptischen Anfalls bei SDH deutlicher höher sein wird, als es im Rahmen unserer Studien vorgelegen hat [5]. Hauptsächlich könnte es am ehesten an der Limitation einer nicht kontinuierlichen Oberflächen-EEG-Ableitung liegen. Daher wäre eine prophylaktische antiepileptische Therapie denkbar, wenn bestimmte Risikoprofile für einen epileptischen Anfall festgelegt werden können.

Temkin et al. hat im Rahmen einer prospektiven doppel-geblindeten Studie untersucht, ob eine prophylaktische antiepileptische Therapie bei SHT die epileptischen Anfälle reduzieren und somit das Outcome verbessern kann. Hier zeigte sich, dass die akut symptomatische Anfallsrate bei Patienten mit prophylaktischer antiepileptischer Therapie signifikant im Vergleich zu Placebo mit RR 0,25 gesenkt werden konnte. Jedoch war die Rate an späten Anfällen nicht unterschiedlich [26]. Daher gibt es von der *American Academy of Neurology und Brain Trauma Foundation* die Empfehlung der Evidenzklasse II, dass bei Patienten mit schwerem SHT Antiepileptika prophylaktisch für eine Woche zur frühen Anfallsreduktion gegeben werden können [27]. Mehr als sieben Tage sollten diese wegen der ausbleibenden positiven Wirkung, nicht gegeben werden. Aufgrund der Nebenwirkung von Phenytoin wurden im Verlauf Studien durchgeführt, welche die Effektivität und Nebenwirkungen von Phenytoin und Leviteracetam verglichen haben [28,29]. Diese zeigten eine vergleichbare Effektivität von Leviteracetam mit deutlich weniger Nebenwirkungen außer gastrointestinalen Problemen. Daher scheint die prophylaktische Therapie ebenfalls mit Levetiracetam bei aSDH möglich zu sein. Jedoch gibt

es bislang keine prospektive randomisierte Studie, die explizit die Erkrankung aSDH untersucht hat. Bezüglich cSDH gibt es kontroverse Meinungen zur prophylaktischen antiepileptischen Therapie, so dass es hierzu keine evidenzbasierte Empfehlung gibt [30–33]. Es scheint vor allem die Auswahl der Risikopatienten eine große Rolle zu spielen, um die Effektivität einer prophylaktischen antiepileptischen Therapie zu maximieren. Neben den Risikofaktoren für epileptische Anfälle bei cSDH, die wir in der Studie OA 4 berichtet haben, gibt es eine wichtige Entität, „*acute-on-chronic*“ SDH, welche entweder als akute Einblutung ins cSDH oder Nachblutung bei cSDH definiert ist [34]. Die Rate von akut symptomatischen Anfällen bei „*acute-on-chronic*“ SDH beträgt 72,4% und von Status epilepticus 10,3% mit einer signifikant erhöhter Mortalität und schlechterer Prognose. Zwar fehlt hier bislang eine prospektive randomisierte Studie, aber eine prophylaktische antiepileptische Therapie bei dieser Entität scheint sinnvoll zu sein.

Auf der Grundlage unserer Arbeiten haben wir uns die Frage gestellt, ob es sinnvoller wäre, statt einer unkontrollierten prophylaktischen antiepileptischen Therapie ein *real-time* EEG Monitoring bei Patienten mit SDH durchzuführen, um eine zeitnahe Diagnostik und kontrollierte Therapie zu ermöglichen. Daher begannen wir im Jahr 2016 mit einer prospektiven Arbeit, „DISEASE“ (*DIagnostic Subdural EEG electrodes And Subdural hEmatoma*), in welcher wir bei Patienten mit SDH eine EEG-Elektrode im Rahmen einer operativen Blutungsentlastung einlegen [35]. Diese soll ein invasives kontinuierliches EEG-Monitoring ermöglichen, um erstens die reale Inzidenz des Anfalls zu detektieren, zweitens die zeitliche Verzögerung der Anfallsdiagnostik zu umgehen und zuletzt unter *real-time* Monitoring eine antiepileptische Therapie besser einzustellen. Des Weiteren hat diese Methode den Vorteil, dass die Haut-Knochen-Barriere und zeitliche Limitation einer Messung nicht vorhanden sind. Die Ergebnisse stehen bislang noch aus. Jedoch könnte dies ein neuer Schritt bei der Therapie von epileptischen Anfällen in Patienten mit SDH sein, um die häufige prognoserelevante Komplikation besser kennenlernen und behandeln zu können.

4. Zusammenfassung und Ausblick

In den der kumulativen Habilitationsschrift zu Grunde liegenden Arbeiten konnte gezeigt werden, dass epileptische Anfälle eine häufige Komplikation bei aSDH und cSDH darstellen, welche mit einer schlechten Prognose assoziiert ist. Verschiedene Prädiktoren für einen epileptischen Anfall konnten identifiziert werden; einheitlich beim aSDH und cSDH sowie Erwachsenen und pädiatrischen Patienten war der GCS als Ausdruck des Schweregrades eines SHTs ein ausschlaggebender Risikofaktor. Zusätzlich wurden weitere Prädiktoren wie Status der Antikoagulation und Zeitpunkt der Operation bei Patienten mit aSDH identifiziert, so dass eine Risikoeinteilung, der *GATE 24-score*, mit den vorgenannten drei Parametern entwickelt wurde, um Patienten mit erhöhtem Risiko eines epileptischen Anfalls schneller diagnostizieren und eine antiepileptische Therapie einleiten zu können. Im Gegensatz dazu war beim cSDH der Status nach Schlaganfall oder das Vorliegen eines Rezidivhämatoms wichtige Prädiktoren für einen epileptischen Anfall und Status epilepticus. Die Patienten mit epileptischen Anfällen hatten ein deutlich schlechteres Outcome sowie eine signifikant erhöhte Mortalität. Um die Prognose dieser Patienten zu verbessern, ist es wichtig, dass man das Risiko der Anfallsentwicklung reduziert. Von allen berichteten Prädiktoren ist jedoch nur ein Parameter optimierbar: Rezidiv eines Hämatoms. Daher haben wir uns in der letzten Arbeit befasst, ein neues postoperatives Management zu entwickeln, um die Rezidivrate des cSDHs zu reduzieren. Das angeleitete Valsalva-Manöver ist eine einfache und kostengünstige Methode, welche in jeder Einrichtung mit ausreichender Compliance von Patienten durchgeführt werden kann. Hierbei wird regelmäßige Inflation von den Patienten in einem selbstgemachten Gerät durchgeführt, um den subduralen Druck zu steigern mit der Konsequenz, dass die Restblutmenge über die eingelegte Drainage gefördert wird. Dies hat zur Folge, dass die Rezidivrate und somit auch das Risiko eines epileptischen Anfalls reduziert wird. Das Ziel der vorliegenden Arbeiten ist zu verdeutlichen, dass epileptische Anfälle und Status epilepticus prognoserelevante häufige Komplikationen bei Patienten mit einem SDH sind. Prädiktive Faktoren sollten dazu helfen, die Patienten mit hohem Risiko eines epileptischen Anfalls schnell zu identifizieren, damit eine adäquate Diagnostik und Therapie oder gegebenenfalls eine Prophylaxe eingeleitet werden kann, um die Prognose und das Outcome der Patienten zu verbessern.

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6. Anhang

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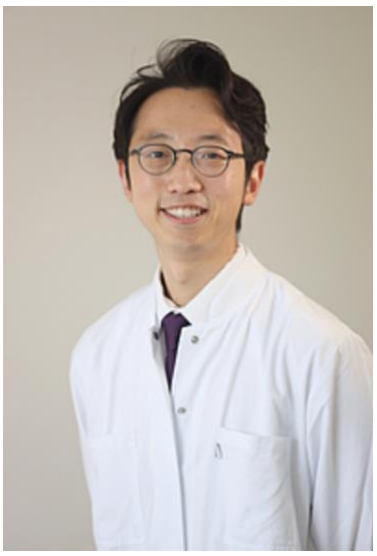
6.2. Curriculum Vitae



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Preise

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03/2021	**FORUN 2021 Förderpreis** “Implantation einer subduralen EEG-Elektrode bei Patienten mit einem schweren Schädel-Hirn-Trauma (DISEASE-TBI-Trial): eine multizentrische prospektive Studie“
06/2021	**DePuySynthes Stipendium der DGNC**

Rostock, den 05.07.2021

6.3. Publikationsliste

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6.4. Selbstständigkeitserklärung

Hiermit erkläre ich, Dr. med. Sae-Yeon Won, dass ich die vorliegende Arbeit selbstständig erfasst habe. Alle hier verwendeten Daten und Ergebnisse anderer sind vollständig aufgeführt und zitiert.

Ich versichere weiterhin, dass die vorliegende Arbeit nicht zuvor bei der hiesigen oder einer anderen Fakultät zur Eröffnung eines Habilitationsverfahrens eingereicht wurde.

Des Weiteren erkläre ich, dass ich deutsche Staatsbürgerschaft besitze und mir die Habilitationsordnung, sowie alle zugehörigen Bestimmungen bekannt sind.

Rostock, 05.07.2021

6.5. Originalarbeiten mit Angabe der Impact-Faktoren

OA1. **Won SY**, Zagorcic A, Dubinski D, Quick-Weller J, Herrmann E, Seifert V, Konczalla J. Excellent accuracy of ABC/2 volume formula compared to computed-assisted volumetric analysis of subdural hematomas. PLoS One. 2018 Jun 26;13(6):e0199809. IF=2,8.

OA2. **Won SY**, Dubinski D, Herrmann E, Cuca C, Strzelczyk A, Seifert V, Konczalla J, Freiman TM. Epileptic Seizures in Patients Following Surgical Treatment of Acute Subdural Hematoma-Incidence, Risk Factors, Patient Outcome, and Development of New Scoring System for Prophylactic Antiepileptic Treatment (GATE-24 score).World Neurosurg. 2017 May;101:416-424. IF=1,7.

OA3. **Won SY**, Dubinski D, Behmanesh B, Strzelczyk A, Seifert V, Konczalla J, Freiman TM. Clinical Relevance of Seizure in Pediatric Patients with Isolated Acute Subdural Hematoma without Parenchymal Brain Injury. J Neurol Surg A. 2019 Jul;80(4):233-239. IF=1,1.

OA4. **Won SY**, Dubinski, Sautter L, Hattingen E, Seifert V, Rosenow F, Freiman TM, Strzelczyk A, Konczalla J. Seizure and status epilepticus in chronic subdural hematoma. Acta Neurol Scand. 2019 Sep;140(3):194-203. IF=2,9.

OA5. **Won SY**, Dubinski D, Behmanesh B, Bernstock JD, Keil F, Freiman TM, Konczalla J, Seifert V, Gessler F. Supervised Valsalva Maneuver after Burr Hole Evacuation of Chronic Subdural Hematomas: A Prospective Cohort Study. J Neurotrauma 2021 Apr 1;38(7):911-917 14. IF= 4,1.

PLOS ONE

RESEARCH ARTICLE

Excellent accuracy of ABC/2 volume formula compared to computer-assisted volumetric analysis of subdural hematomas

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Abstract

Background

Subdural hematoma (SDH) is a common disease associated with high morbidity, which is becoming more prominent due to the increasing incidence. Decision for a surgical evacuation is made depending on the clinical appearance and the volume of SDH, wherefore it is important to have a simple 'bedside' method to measure and compare the volume of SDH.

Objective

The aim of the study was to verify the accuracy of the simplified ABC/2 volumetric formula to determine a valuable tool for the clinical practice.

Methods

Preoperative CT-scans of 83 patients with SDHs were used for the computer-assisted volumetric measurement via BrainLab® as well as the ABC/2 volumetric measurement. A = largest length (anterior to posterior) of the SDH; B = maximum width (lateral to midline) 90˚ to A; C = maximum height (coronal plane or multiplication of slices) of the hematoma. These measurements were performed by two independent clinicians in a blinded fashion. Both volumes were compared by linear regression analysis of Pearson and Bland-Altman regression analysis.

Results

Among 100 SDHs, 53% were under an 47% were over 100cm^3 showing a well distribution of the hematoma sizes. There was an excellent correlation between computer-assisted volumetric measurement and ABC/2 (R^2 = 0.947, p<0.0001) and no undesirable deviation and trend were detected (p = 0.101; p = 0.777). A 95% tolerance region of the ratios of both methods was [0.805–1.201].

Conclusion

The ABC/2 method is a simple and fast bedside formula for the measurement of SDH volume in a timely manner without limited access through simple adaption, which may replace the computer-assisted volumetric measurement in the clinical and research area. Reason for the good accuracy seems to be the spherical form of SDH, which has a similarity to a half ellipsoid.

Introduction

Subdural hematoma (SDH) is a common disease and is becoming more prominent due to increasing incidence as well as cost factor national wide [1,2]. The decision for a surgical evacuation is made by the clinical appearance, mass effect with brain herniation and the volume of SDH, wherefore it is important to have a simple bedside method to measure the volume of SDH in clinical routine. Furthermore, an easy and valid method of hematoma volume is essential to make studies comparable. Previously, several studies investigated and reported the accuracy of the simplified ellipsoid volumetric formula, ABC/2, to measure intracerebral hemorrhage (ICH) as well as epidural hematoma (EDH), whereas to the best of our knowledge, there have been only one study observing the formula regarding SDH in small number of patients [3–7]. Since the geometric form of SDH differs from an ICH or EDH, which are ellipsoidal, we hypothesized an inaccuracy of ABC/2 for the volumetric measurement of SDH. Therefore, the aim of the study was to compare the ABC/2 formula to a computer-assisted volumetric analysis and in case of an inaccuracy to create a new formula for SDH volume measurement.

Subjects and methods

This study was approved by the clinical ethic committee of the university Frankfurt (EK Nr.509/15). The ethic committee waived the need for patient content. In this study, we analysed 82 patients with chronic SDH from 2016 to 2017. Both sided SDH was accounted as two SDHs resulting in a review of 100 subdural hematomas. The preoperative CT-scans at admission were performed in a 5mm slice thickness and were used for both volumetric measurements: the computer-assisted measurement and ABC/2. Each method was used by an independent clinician in a blinded fashion. Patients with combined interhemispheric SDH or missing radiological data were excluded.

For the ABC/2 method axial CT planes were used. The largest length (anterior to posterior) to each corner of the SDH was defined as A (cm), the maximum width (lateral to midline) 90˚ to A in the same slice as B (cm) and the maximum height of the hematoma as C (cm). For the calculation of the height, the number of slices with visible hematoma was multiplied by the thickness (e.g. 5mm) of the CT-scan or a coronal plane was used. The hematoma volume (cm^3) was obtained by multiplying A, B and C and dividing it by 2 (Fig 1A).

For the computer-assisted measurement, the BrainLab® elements software (Brainlab Germany Headquarters, Munich, Germany) was used. This software can be used for radiosurgical therapy planning, intraoperative navigation and preoperative segmentation including multiplanar volume definition. The hematoma margins were hand traced and the volume was automatically calculated (Fig 1B and 1C).

Linear regression analysis of Pearson and Bland-Altman regression analysis on log-scale were used to determine the correlation between those methods [8].

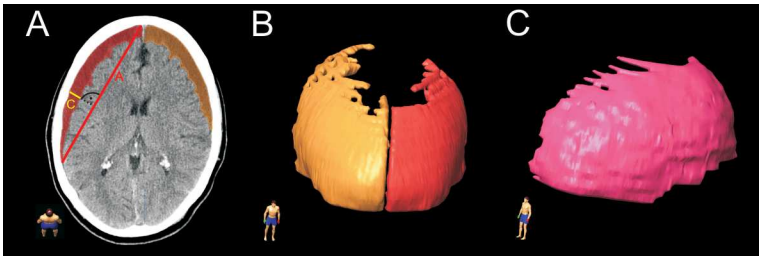

Fig 1. A. Preoperative axial CT-scan with both sided subdural hematomas (SDH). Computer-assisted volumetric measurement was performed by hand tracing each hematoma form in each slice as shown in red and orange colour. ABC/2 measurement technique was performed as following: A is the length connected each corner of the SDH, B is 90˚ to A and C is the height calculated by the slice thickness with visible hematoma. **B.** 3D frontal reconstruction of computer-assisted volumetric measurement of both sided SDH. **C.** 3D lateral reconstruction of computer-assisted volumetric measurement of single sided SDH.

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Results

Among 100 SDHs, 53 SDHs (53%) were under and 47 SDHs (47%) were over 100cm^3 showing well distributed hematoma size. The mean volume was 106.3±47.3cm^3 in the ABC/2 technique whereas 104.6±47.7cm^3 in the computer-assisted volumetric measurement showing no significant difference. In the linear regression analysis, there was a highly significant correlation between ABC/2 and computer-assisted values (R^2 = 0.934, slope = 0.975) (Fig 2A). The same result was also observed in the Bland-Altman regression analysis between the log of ABC/2 and the log of the computer-assisted values (R^2 = 0.947, p<0.0001) (Fig 2B). Bland and Altmann regression revealed no undesirable deviation between the geometric mean of ABC/2 and the computer-assisted measurements and the ratios of these values (p = 0.101) and no undesirable trend (p = 0.777). A 95% tolerance region of the ratios of both methods was [0.805–1.201].

Discussion

Against our initial hypothesis there was an excellent correlation between ABC/2 formula and computer-assisted volumetric measurement of SDH supporting the use of ABC/2 in the clinical practice and research. In addition, the formula had no limited access to the size of SDH volume.

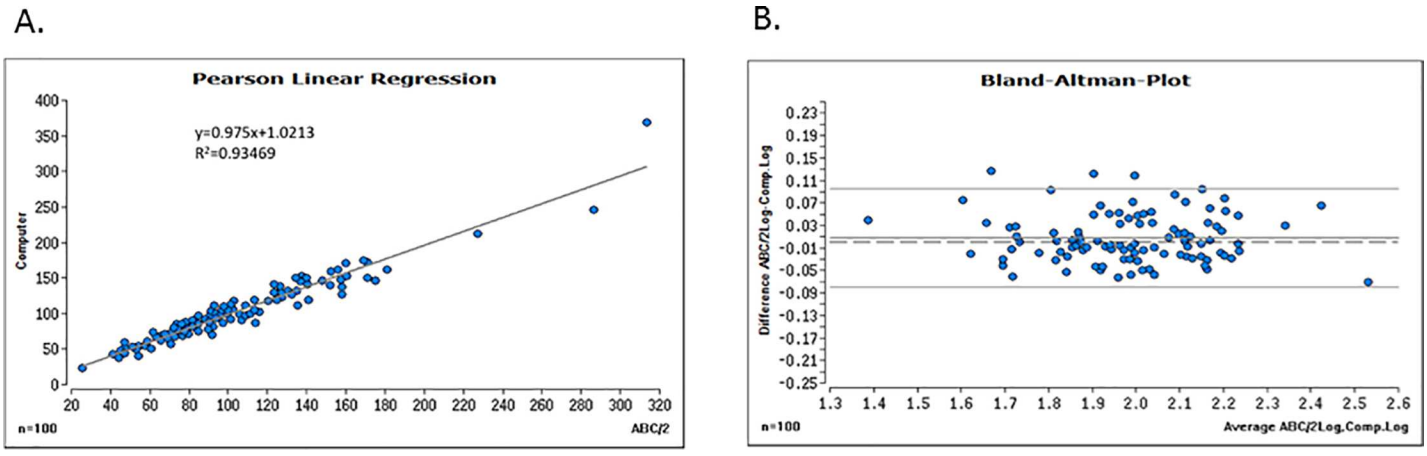

Fig 2. A. Pearson Linear regression analysis between ABC/2 and computer-assisted volumetric measurement. **B.** Bland-Altman regression analysis between log of ABC/2 and log of computer-assisted volumetric measurement.

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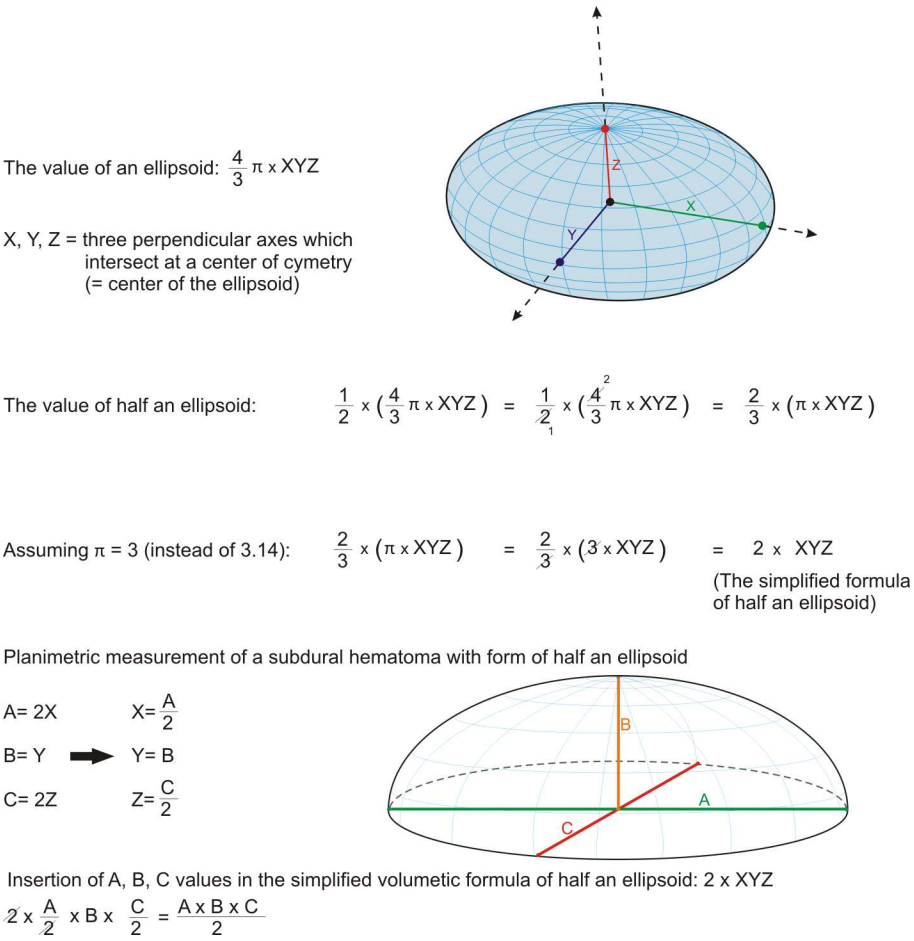

Fig 3. Mathematical derivation of the ABC/2 formula from a half ellipsoid volumetric formula.

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At this point, the relevance of this simplified ABC/2 formula in patients with SDH should be mentioned. Previously Kothari et al. analyzed the timely manner of each volumetric measurement indicating that the simplified formula required less than one minute, whereas the computer-assisted volumetric analysis required about 15 factors more time [4]. There is a well-known phrase in the treatment of stroke, "time is brain". However, the time is also essential in case of any traumatic brain injuries like SDH since an accurate initiation of acute management can reduce morbidity and improve further prognosis [2,9]. Additionally, the formula can be used as a helpful tool for the further evaluation of SDH residuum at follow-up and further studies to compare each volumes without any specific software. In certain circumstances, it is not simple to compare the development of SDH volume due to the change of geometric SDH form, varying thickness of scans or slice variations. Indeed measuring only the maximum thickness of the hematoma might illustrate us false information which could result in an unnecessary surgical treatment. Therefore, by using the simplified formula, the comparison could be made promptly and ease the further decision.

For the volumetric measurement of ICH, several studies have been estimating using different type of formula, however, only the formula for an ellipsoid have been shown to correlate well with plan metric techniques [4,10–12]. In addition, this formula was approved for several other entities like EDH, vestibular schwannomas and gliomas, whereas for cerebral

arteriovenous malformation a significant discrepancy was identified, possibly due to the heterogeneous group of lesions [7,13–15]. To date, there is only one study published, GUSTO-1 trial, showing the accuracy of ABC/2 in the volumetric measurement of SDH similar to our study [4]. However in this study, the mean volume of the SDH (68cm^3) and the sample size (n = 40) were small. Since there could be a discrepancy concerning the volume, we included well distributed size of the SDH (range 57–363 cm^3), which showed no limited use of this formula. Furthermore by increasing the sample size, we tried to obtain more statistical power in order to replace the computer-assisted volumetric measurement,

Against our initial expectation we questioned, why the volume of SDH would fit into this formula for an ellipsoid: The simple explanation for this might be the spherical form of SDH, which has a similarity to a half ellipsoid. Detailed information is described below in Fig 3.

There are some limitations to mention in this study. We excluded SDH with interhemispheric components, since those geometric forms are completely different than lateral SDH. There might be other formula to add those components; however in this study we just focused on the lateral component. Secondly, we used CT-scans with 5mm thickness slices. The calculation of the hematoma size could be adjusted depending on the slice thickness, but there might be some discrepancy using CT-scans with thicker slices.

Conclusion

In this study, we identified that the ABC/2 method is a simple and excellent bedside formula, which can be used for the volume measurement of SDH without limited access in order to initiate acute management and decision in a timely manner. Reason for the good accuracy seems to be the spherical form of SDH, which has a similarity to a half ellipsoid.

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Author Contributions

Conceptualization: Sae-Yeon Won, Daniel Dubinski, Volker Seifert, Juergen Konczalla.

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Epileptic Seizures in Patients Following Surgical Treatment of Acute Subdural Hematoma—Incidence, Risk Factors, Patient Outcome, and Development of New Scoring System for Prophylactic Antiepileptic Treatment (GATE-24 score)

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OBJECT: **Clinically evident or subclinical seizures are common manifestations in acute subdural hematoma (aSDH); however, there is a paucity of research investigating the relationship between seizures and aSDH. The purpose of this study is 2-fold: determine incidence and predictors of seizures and then establish a guideline in patients with aSDH to standardize the decision for prophylactic antiepileptic treatment.**

METHOD: **The author analyzed 139 patients with aSDH treated from 2007 until 2015. Baseline characteristics and clinical findings including Glasgow Coma Scale (GCS) at admission, 24 hours after operation, timing of operation, anticoagulation, and Glasgow Outcome Scale at hospital discharge and after 3 months were analyzed. Multivariate logistic regression analysis was performed to detect independent predictors of seizures, and a scoring system was developed.**

RESULTS: **Of 139 patients, overall incidence of seizures was 38%, preoperatively 16% and postoperatively 24%. Ninety percent of patients with preoperative seizures were seizure free after operation for 3 months. Independent predictors of seizures were GCS <9 (odds ratio [OR] 3.3), operation after 24 hours (OR 2.0), and anticoagulation (OR 2.2). Patients with seizures had a significantly higher rate of unfavorable outcome at hospital discharge ($P = 0.001$) and in 3-month follow-up ($P = 0.002$). Furthermore, a score system (GATE-24) was developed. In patients with GCS <14, anticoagulation, or surgical treatment 24 hours after onset, a prophylactic antiepileptic treatment is recommended.**

CONCLUSION: **Occurrence of seizures affected severity and outcomes after surgical treatment of aSDH. Therefore seizure prophylaxis should be considered in high-risk patients on the basis of the GATE-24 score to promote better clinical outcome.**

INTRODUCTION

Epileptic seizures are a common clinical manifestation in patients with subdural hematomas (SDH). In particular, patients with acute SDH (aSDH) have an even higher incidence of seizures, approximately 24%–36%.[1-3] The prognosis of aSDH is influenced by multiple factors such as age; Glasgow Coma Scale (GCS); pupillary inequality; computed tomography (CT) findings (hematoma size, midline shift, associated intradural lesion, compression of basal cisterns); and time until surgical treatment. However, the occurrence of seizures was described as an independent prognostic factor for unfavorable outcome.[2,4-7,3]

Key words
- Acute subdural hematoma
- Epilepsy
- Functional outcome
- Post-traumatic seizures
- Prophylactic antiepileptic treatment
- Risk factors

Abbreviations and Acronyms
aSDH: Acute subdural hematoma
AED: Antiepileptic drugs
AUC: Area under curve
BTF guidelines: Brain Trauma Foundation Surgical Guidelines
CT: Computed tomography
EEG: Electroencephalography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
OR: Odds ratio
TBI: Traumatic brain injury

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Therefore it is crucial to identify and treat high-risk patients as soon as possible.

Several studies have examined predictors and outcome of seizures in patients with traumatic brain injury (TBI), but specific data for seizures in occurrence of an aSDH are still lacking. This is an important issue because the risk for epileptic seizures is different depending on the entities of TBI.[8] Previous studies reported aSDH, skull fracture, loss of consciousness, and brain contusion as independent predictors for seizures in patients with TBI.[9,10] In particular, severe TBI was shown to be a major risk factor for early epileptic seizures and to have a negative influence on early functional outcome.[9] Therefore the American Academy of Neurology and Brain Trauma Foundation Surgical Guidelines (BTF guidelines) recommend the use of antiepileptic drugs (AEDs) in the first week following TBI.[11,12] Regarding isolated aSDH, one retrospective study by Rabinstein et al[2] reported some risk factors for postoperative seizures like low GCS at admission/after surgery and craniotomy, but to date there is no precise standardized guideline available for the use of primary prophylactic AED treatment in isolated aSDH. Indeed, there are controversial clinical practices for the use of prophylactic treatment in different hospitals and decisions are made by clinic-specific standards or instinctively. One of the major criteria for starting antiepileptic drugs empirically is the decision to operate on an aSDH.

Consequently, a risk profile definition would be helpful in clinical practice to identify high-risk patients who may benefit from primary prophylactic AED treatment. We performed a retrospective single-center analysis to identify outcome and high-risk patients for epileptic seizures with aSDH in general, as well as in the preoperative and postoperative phases. In addition, a new score system was developed to ease and standardize clinical decision in the use of prophylactic AED in aSDH.

METHODS

Patients and Data Collection

This study was approved by the Clinical Ethics Committee of the University of Frankfurt (Nr.509/15). For this type of study, formal consent is not required.

Using an electronic patient database, all patients older than 18 years old with an aSDH treated at the Neurosurgical Department of the Goethe University Hospital Frankfurt between March 2007 and December 2015 were identified. Inclusion criterion was the primary admission diagnosis of aSDH. Patients with hospital discharge in <24 hours or missing radiologic data were excluded (**Figure 1**). All patients were treated per BTF guidelines except for the prophylactic use of AED.[12]

All medical records were examined, and the following parameters were collected: age at admission; gender; timing of operation; trauma; hematoma side (right, left, bilateral); hematoma volume; midline shift; width of hematoma; GCS at admission; surgical treatment (craniotomy, craniectomy, burr hole, conservative); GCS 24 hours after surgical treatment; GCS at hospital discharge; occurrence of preoperative and postoperative epileptic seizure; epileptiform discharges in electroencephalography (EEG); previous stroke; previous seizure; treatment with anticoagulation; rebleeding; and functional outcome at hospital discharge and in 3 months' follow-up.

Radiologic measurements were performed using preoperative CT scans. For hematoma volume measurements, the volume estimating formula ABC/2 was used.[13] In the case of bilateral hematomas, both volumes were added together. For midline shift and width of hematoma, the maximum diameter was measured. In case of clinically suspected epileptic seizures, we assessed the surface EEG recording. EEG recordings were reviewed by experienced, EEG-board-certified neurologists who were blind to the outcome. Functional outcome was evaluated by Glasgow Outcome Scale (GOS) at hospital discharge and at 3 months' follow-up. GOS 1–3 was defined as an unfavorable functional outcome, and GOS 4–5 was defined as a favorable functional outcome.

STUDY DESIGN

This study was a retrospective analysis in a single center observing patients with aSDH. The aims of the study were 1) to observe the incidence of epileptic seizures in patients with aSDH, 2) to identify specific risk factors of epileptic seizures in aSDH preoperatively and postoperatively, 3) to compare functional outcome between the seizure and nonseizure groups, and 4) to develop a scoring system as a guideline for use of prophylactic antiepileptic treatment.

We performed a univariate and multivariate analysis between seizure and nonseizure groups in patients with aSDH to evaluate the incidence and general risk factors of seizure. Patients were assigned to the seizure group in the presence of ictal patterns on EEG, a clinical manifestation of a seizure, or a clinical suspicion of a seizure combined with interictal epileptiform discharges. Patients with interictal epileptiform discharges only did not qualify for the seizure group as interictal discharges are recorded frequently in patients with acute brain damage.[14,15,16] For the multivariate analysis, parameters with a P value <0.1 in univariate analysis were selected. Functional outcomes between the seizure and nonseizure groups were compared. Furthermore, a subgroup analysis with patients with preoperative or postoperative seizures was conducted. On the basis of the identified independent risk factors of seizures, which may influence the decision for or against prophylactic antiepileptic treatment, predictive parameters were integrated in a score system for practical use.

STATISTICS

Graphpad prism (version 6.0, GraphPad Software Inc., La Jolla, California, USA) and IBM SPSS Statistics (version 22, IBM Corp., Armonk, New York, USA) were used for data analysis. Univariate and multivariate analyses were performed. For parametric parameters, an unpaired t-test was used. For nonparametric parameters, variables were analyzed in a contingency table using Fisher's exact test. To assess the impact of the variables, odds ratios (ORs) with 95% confidence intervals (CI_{95}) were calculated. In addition, for the defined risk factors of epileptic seizures, we performed a stepwise multivariable logistic regression analysis (Nagelkerke's $R^2 = 0.2$). The obtained weighting scheme of the final step was slightly simplified to derive the GATE-24 score. ROC-analysis was performed, and the cutoff was defined by the Youden index. Sensitivity and specificity were calculated with CI_{95}. All tests were 2-sided, and $P \leq 0.05$ was considered to be statistically significant. In case of multivariate analysis, $P \leq 0.1$ was considered to be statistically significant.

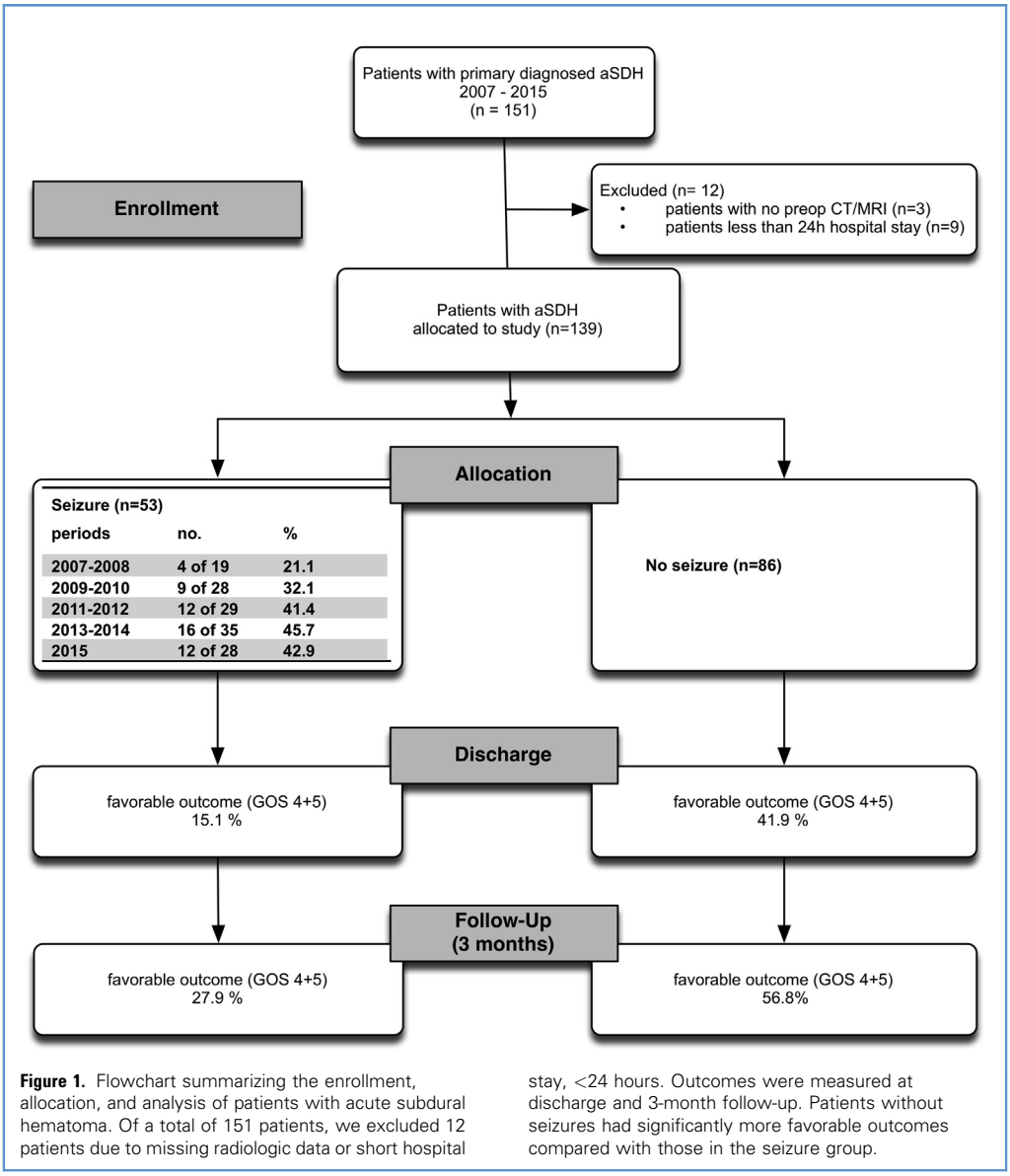

Figure 1. Flowchart summarizing the enrollment, allocation, and analysis of patients with acute subdural hematoma. Of a total of 151 patients, we excluded 12 patients due to missing radiologic data or short hospital stay, <24 hours. Outcomes were measured at discharge and 3-month follow-up. Patients without seizures had significantly more favorable outcomes compared with those in the seizure group.

RESULTS

In total, 139 aSDHs without other brain injuries were included between 2007 and 2015 (Figure 1). The mean age of the patients was 72.7 ± 14.3, and 45 of them (32.4%) were female. The CT scan at admission showed mean aSDH volume of 96.6 ± 51.5 cm^3 and midline shift of 9.0 ± 6.1 mm. There was an even distribution between the right and left hematoma side, and 9 patients (6.4%) had bilateral hematomas. More than 50% of patients had severe aSDH expressed by GCS ≤8 at admission and 24 hours after surgical treatment. As comorbidities, 19 patients (13.7%) had previously suffered from a stroke, 3 patients (2.2%) had a history of seizures, and 88 patients (63.3%) were anticoagulated. About 21% had experienced a rebleeding of surgically treated aSDH during the hospital stay (Table 1).

Incidence of Seizures in Patients with aSDHs

In total, 53 patients (38.1%) were assigned to the seizure group. Among them, 21 of 53 patients (39.6%) had preoperative seizures; 34 of 53 patients (64.2%) had postoperative seizures, and 2 patients (3.8%) had preoperative and postoperative seizures. After surgical treatment, 90% of patients (20 of 22 patients) with preoperative seizures were seizure free for 3 months. In 2-year intervals, the incidence of seizures constantly increased, 21.1% between 2007 and 2008 until 45.7% between 2013 and 2014. The incidence of seizure in 2015 was 42.9%. Simultaneously, the EEG diagnostic rate of epileptiform discharges increased: 10.5% (2007/2008), 14.3% (2009/2010), 34.5% (2011/2012), 37.1% (2013/2014), and 42.9% in 2015 (total EEG diagnostic rate: 28.8%). All EEG diagnostics were performed within 1 week after onset.

Table 1. Overall Incidence and Risk Factors for Epileptic Seizure in Patients with Acute Subdural Hematoma*

Variable	All	Seizure or Epileptiform Discharge (%)	No Seizure or Epileptiform Discharge (%)	Univariate Analysis		Multivariate Analysis	
				P Value	OR [CI 95%]	*P* Value	OR [CI 95%]
Number of patients	139	53 (38.1)	86 (61.9)				
Age (years)	72.7 ± 14.3	74.4 ± 14.7	71.7 ± 14.7	ns			
Timing of operation (days)	0.6 ± 1.4	0.8 ± 1.7	0.5 ± 1.2	ns			
Operation >24 hours	33	17 (53.1)	16 (18.6%)	0.09	2.1 [0.94–4.6]	0.09	2.0 [0.9–4.5]
Gender (female)	45 (32.4)	16 (30.2)	29 (33.7)	ns			
Trauma	91 (65.5)	34 (64.2)	57 (66.3)	ns			
Hematoma side							
Left	60 (43.2)	23 (43.4)	37 (43)	ns			
Right	70 (50.4)	26 (49.1)	44 (51.2)	ns			
Both	9 (6.4)	4 (7.5)	5 (5.8)	ns			
Mean SDH volume in cm^3 ± SD	96.6 ± 51.5	100.4 ± 45.3	94.2 ± 55.0	ns			
Mean midline shift in mm ± SD	9.0 ± 6.1	9.1 ± 6.6	9.0 ± 5.8	ns			
Width of aSDH ≥1.4 cm	93 (66.9)	41 (77.4)	52 (60.5)	0.04	2.2 [1.0–4.9]	ns	
GCS ≤8, at admission	73 (52.5)	37 (69.8)	36 (41.9)	0.001	3.2 [1.6–6.6]	ns	
GCS ≤8, 24 hours postoperation	75 (54.0)	38 (71.7)	37 (43)	0.002	3.4 [1.6–7.0]	0.002	3.3 [1.6–7.1]
Operation	115 (82.7)	48 (90.6)	67 (77.9)	0.07	2.7 [1.0–7.8]	ns	
Craniotomy	83 (59.7)	37 (69.8)	46 (53.5)	0.07	2.0 [1.0–4.2]	ns	
Craniectomy	32 (23.0)	11 (20.8)	21 (24.4)	ns			
Previous stroke	19 (13.7)	7 (13.2)	12 (14)	ns			
Previous seizure	3 (2.2)	1 (1.9)	2 (2.3)	ns			
Anticoagulation	88 (63.3)	40 (75.5)	48 (55.8)	0.03	2.4 [1.1–5.2]	0.047	2.2 [1.0–4.9]
Rebleeding	29 (20.9)	9 (17.0)	20 (23.3)	ns			

OR, odds ratio; CI, confidence interval; ns, not significant; SDH, subdural hematoma; SD, standard deviation; aSDH, acute subdural hematoma; GCS, Glasgow Coma Scale.
*All numbers represent the number of patients, the percentage in parentheses.

Among the patients with an EEG recording, 45% of patients had ictal or interictal activity on EEG.

Risk Factors for Seizures in Patients with aSDH

Predictors of the presence of seizures or epileptiform discharges on EEG are illustrated in Table 1. GCS ≤8 at admission (OR 3.2), GCS ≤8 24 hours after operation (OR 3.4), width of aSDH ≥1.4 cm (OR 2.2), and previous treatment with anticoagulants (OR 2.4) were independently associated with the occurrence of seizures in patients with aSDH. Furthermore, we distinguished between seizures of preoperative and postoperative nature. In the subgroup analysis of postoperative seizures, the main results (GCS ≤8 at admission [OR 2.6]/24 hours after operation [OR 2.8] and anticoagulation [OR 2.9]) did not differ substantially, however, surgical treatment via operation was an additional predictor of postoperative seizures (OR 2.5) (Table 2). In contrast, delayed burr-hole trepanation, which was possible in 12.9% of cases, was a negative predictor for seizures (OR 7.0). In the subgroup analysis of preoperative seizures, besides low GCS at admission (GCS ≤8; OR 2.6; CI_{95} [1.1–5.8]; $P = 0.007$), the timing of operation was a significant parameter for occurrence of seizures (seizure group vs. nonseizure group: 1.3 ± 2.5 days vs. 0.5 ± 1.2 days; $P = 0.04$).

On the basis of identified risk factors (operation >24 hours, widths of aSDH ≥1.4 cm, GCS ≤8 at admission, GCS ≤8 24 hours postoperation, operation, anticoagulation), we performed a logistic regression analysis to verify independent predictors for epileptic seizures. Low GCS 24 hours after operation (OR 3.3; Cl_{95} [1.6–7.1]; $P = 0.002$), timing of operation ≥1 day (OR 2.0; CI_{95} [0.9–4.5]; $P = 0.09$), and existing anticoagulation (OR 2.2; CI_{95} [1.0–4.9]; $P = 0.05$) were independently associated with the occurrence of seizures in the multivariate analysis. Age, sex, trauma, hematoma volume and side, midline shift, previous stroke, or seizures were not significant predictors for either preoperative or postoperative seizures.

Table 2. Subgroup Analysis of Incidence and Risk Factors for Postoperative Epileptic Seizure in Patients with Acute Subdural Hematoma*

Variable	Postoperative Seizure or Epileptiform Discharge (%)	No Seizure or Epileptiform Discharge (%)	Univariate Analysis	
			P Value	OR [CI 95%]
Number of patients	34 (28.3)	86 (71.7)		
Age (years)	77.1 ± 12.1	71.7 ± 14.7	ns	
Timing of operation (days)	0.6 ± 1.0	0.5 ± 1.2	ns	
Sex (female)	10 (29.4)	29 (33.7)	ns	
Trauma	22 (64.7)	57 (66.3)	ns	
Hematoma side				
Left	15 (44.1)	37 (43)	ns	
Right	17 (50)	44 (51.2)	ns	
Both	2 (5.9)	5 (5.8)	ns	
Mean SDH volume in cm^3, ±SD	101.0 ± 47.9	94.2 ± 55.0	ns	
Width SDH >14 mm				
Mean midline shift in mm, ±SD	9.1 ± 6.7	9.0 ± 5.8	ns	
GCS ≤8, at admission	22 (64.7)	36 (41.9)	0.03	2.6 [1.1—5.8]
GCS ≤8, 24 hours postoperation	24 (70.6)	37 (43)	0.008	3.2 [1.4—7.5]
Operation	32 (94.1)	67 (77.9)	ns (0.06)	4.5 [1.0—20.7]
Craniotomy	25	46 (53.5)	ns (0.06)	2.4 [1.0—5.8]
Craniectomy	7	21 (24.4)	ns	
Previous stroke	4 (11.8)	12 (14)	ns	
Previous seizure	0 (0)	2 (2.3)	ns	
Anticoagulation	27 (79.4)	48 (55.8)	0.02	3.1 [1.2—7.8]
Rebleeding	7 (20.6)	20 (23.3)	ns	

OR, odds ratio; CI, confidence interval; ns, not significant; SDH, subdural hematoma; SD, standard deviation; GCS, Glasgow Coma Scale.
*All numbers represent the number of patients, the percentage in parentheses. Unfavorable functional outcome was defined as GOS1-3.

Functional Outcome on Hospital Discharge and at 3 Months' Follow-Up

Evaluations of functional outcome at hospital discharge and in a 3-month follow-up are displayed in Figure 2 and Table 3. In total, 84.9% of patients with aSDH survived at hospital discharge. Patients with seizures had significant unfavorable functional outcomes (GOS 1—3) compared with patients without seizures at hospital discharge (P = 0.001). Similar to previous results, the seizure group had a significantly higher risk for unfavorable outcome compared with the nonseizure group after 3 months' follow-up (P = 0.003). The overall mortality in 3 months was 30.6%. The seizure group had a significantly higher mortality rate compared with the nonseizure group (41.9% vs. 23.1%, P = 0.05).

GATE-24 Score as Guideline for Use of Prophylactic Antiepileptic Treatment

We performed a receiver operating characteristic analysis with the previously identified independent predictors through multivariate analysis for epileptic seizures (timing of operation, GCS 24 hours after operation, anticoagulation). The results are shown in Figure 3. We developed a new scoring system (GATE-24) considering each statistic power of the parameters (Table 4): **G**CS, **A**nticoagulation, **T**iming of operation <24 hours, **E**pileptic treatment not required ≥ **24**P. The most significant parameter among those 3 was the GCS score 24 hours after operation. The cutoff was measured at 24 points, and the AUC, as the indicator of its diagnostic power, was measured at 0.71, 95% CI [0.62—0.80]. In addition, measuring the sensitivity and specificity of the GATE-24 score, the predictive value of a positive test result was 59.3% and the predictive value of a negative test result was 73.6%.

DISCUSSION

In the present study, the incidence of preoperative and postoperative epileptic seizures was measured and predictors for aSDH-associated seizures were identified and integrated in a novel

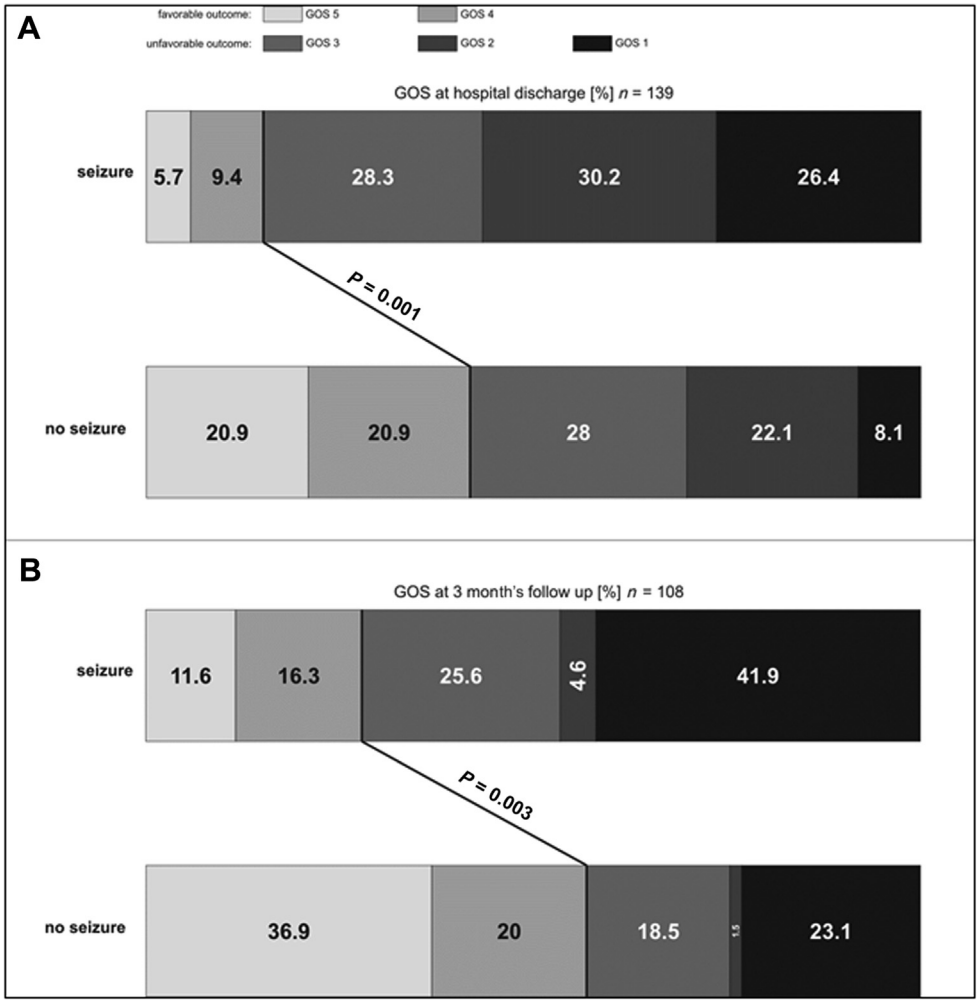

Figure 2. (**A**) Comparison of functional outcome between seizure and nonseizure group via Glasgow Outcome Scale (GOS) at hospital discharge. (**B**) Functional outcome in seizure and nonseizure groups at 3-month follow-up.

score system to ease the decision for the use of prophylactic antiepileptic treatment.

The overall incidence of seizures was 38%, preoperatively 16% and postoperatively 24%, similar to previously published data.[1,2,17-20] A small percentage (1.4%) of the patients had both preoperative and postoperative epileptic seizures. Interestingly, the incidence of epileptic seizures increased dramatically from 2007–2015. This may be due to the alertness toward epileptic seizures or subclinical seizures and both increased rates and repeated EEG recordings over time. Rudzinski et al[21] examined EEG findings in 24 patients with aSDH and found that 87% of those patients had epileptiform abnormalities, implicating a

Table 3. Unfavorable Functional Outcome in Seizure and Nonseizure Groups (Seizure Group had Significant Unfavorable Functional Outcome at Hospital Discharge, as Well as 3 Months' Follow-Up)

	All	Seizure	No Seizure	*P* Value	OR [CI 95%]
Unfavorable functional outcome at hospital discharge*	95 of 139 (68.3)	45 of 53 (84.9)	50 of 86 (58.1)	0.001	4.05 [1.70–9.62]
Unfavorable functional outcome in 3-month follow-up*	59 of 108 (54.6)	31 of 43 (72.1)	28 of 65 (43.1)	0.003	3.41 [1.49–7.81]

OR, odds ratio; CI, confidence interval.
*All numbers represent the number of patients, the percentage in parentheses.

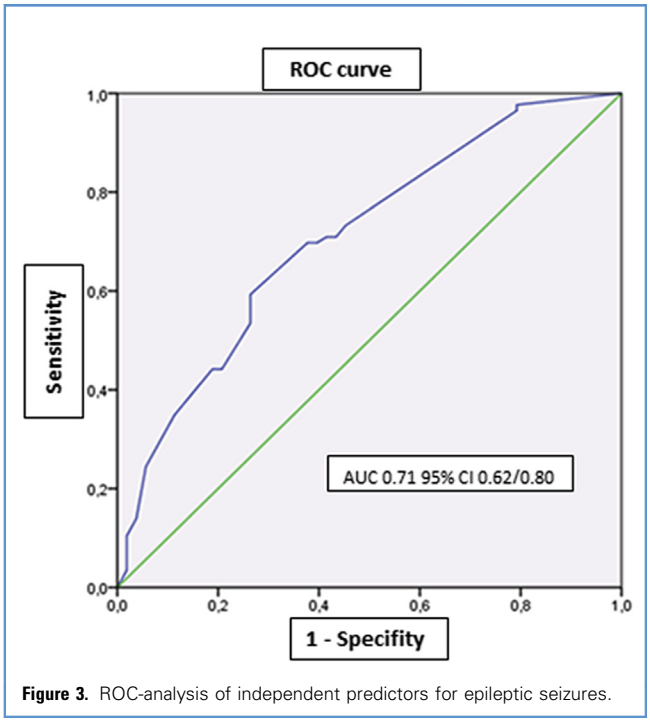

Figure 3. ROC-analysis of independent predictors for epileptic seizures.

higher incidence of epileptic seizures than observed in clinical routine. Among them, 12% of patients had focal or multifocal subclinical electrographic seizures without apparent clinical manifestation.[21] These subclinical seizures may cause subtle cognitive and behavioral interference and are known to increase the likelihood of recurrent epileptic seizures.[22] Thus it is important to identify and treat subclinical seizures. For the clinical routine, regular noninvasive EEG recordings as a routine diagnostic in patients with aSDH might help avoid overlooking seizures; however, there are limitations because of the surface barrier and limited recording time. An invasive EEG diagnostic via subdural grids might be an alternative to accurately detect subclinical seizures in unconscious patients in the early phase because a prospective study observing complications in patients with EEG grid electrodes reported a low complication rate of 3.7% intracranial bleeding and 0.7% wound infection.[18] Further prospective studies are therefore needed to evaluate a possible benefit of invasive or noninvasive EEG diagnostics in patients with aSDH.

Table 4. GATE-24 Score: Indicator for Prophylactic Antiepileptic Drug Application

GATE-24 Score	
Variable	**Points**
GCS 24 hours after operation	GCS score
Anticoagulation: no	5
Timing of operation<24 hours	5
Epileptic treatment not required	≥ **24** P

*All numbers represent the number of patients, the percentage in parentheses.
GCS, Glasgow Coma Scale; p, point.

We identified several predictors for preoperative and postoperative seizures: low GCS at admission (≤8), low GCS (≤8) 24 hours after operation, delayed operation time (≥1 day), width of aSDH ≥1.4 cm, craniotomy, and existing anticoagulation. Similar results were identified previously by Rabinstein et al.[2] Several studies evaluated epileptic seizures after surgical treatment.[17,23-25] The incidence of seizures following supratentorial craniotomy for nontraumatic pathology was estimated between 15% and 20% and 7% and 11% within 7 days after craniectomy in patients with TBI.[17,23,24] The seizures may be partly due to the primary pathology and severity of TBI, yet cerebral manipulation and intraparenchymal injury via surgery may also have an influence. Englander et al[25] identified the intracranial surgery as an independent risk factor for late epileptic seizures. Otherwise, there are contrary opinions about the decompressive surgical treatment. The mass effect of aSDH, characterized by width of aSDH, has compressive effects causing functional derangement of contralateral or mesial cerebral hemisphere resulting in neuronal excitability.[21] Furthermore, hemoglobin with the blood compounds and its degradation products are known to be highly epileptogenic due to its irritation of the cortical surface.[25] On the basis of pathophysiology, the decompressive surgical treatment might have a positive effect in reducing epileptic seizures. Indeed, 90% of patients with preoperative epileptic seizures were seizure free after the operation. Therefore defining "operation" as a predictor for epileptic seizures in general is ambivalent. The fact is that surgical treatment reduces preoperative epileptic seizures; however, it is an additional risk factor for postoperative epileptic seizures. Differentiating between surgical treatments, patients treated by delayed burr-hole trepanation had the lowest risk for postoperative seizures compared with open surgical treatment, probably due to the combination of both effects as mentioned earlier. These findings implicate that patients would profit from an immediate operation if surgical treatment via craniotomy or craniectomiy *is required*, but if it is not urgent, patients would profit from a burr-hole operation at a later time.

Severe traumatic injury (GCS ≤8) is a well-known predictor for epileptic seizure.[9,10,20,26] In a large population-based study ($n = 4541$), the most significant risk factors for seizures were subdural hematoma and loss of consciousness.[10] These results correlate well with our results reporting association between low GCS (GCS ≤8) as a marker of severe aSDH and seizures. Furthermore, existing anticoagulation was an independent risk factor for seizures. In our study it was not significantly associated with rebleeding rate, but several studies reported on the extent of hematoma and frequent rebleeding rate in patients with anticoagulation.[27-29] Moreover, the blood fluidity is changed by anticoagulation resulting in a larger distribution and contact area of blood with the cortical surface, which might be the pathophysiologic mechanism for the increased risk for seizures.[25] To date there have been no studies assessing the pathophysiologic association between anticoagulation and seizures.

In general, the mortality in patients with aSDH ranges from 22% up to 60%.[26,30,31,32] In the present study, the overall mortality

rate was 15% at hospital discharge and 30% at 3 months follow-up, similar to previous results. Patients with epileptic seizures had unfavorable outcomes, significantly more often compared with nonseizure patients (mortality 42% vs. 23% in 3 months' follow-up). Previously, epileptic seizures were reported as an independent marker for poor functional outcome.[2,33] However, in other studies, only early functional outcome was affected and the initial finding became less significant over time.[9,11] Even under antiepileptic treatment, the long-term outcome was not significantly different.[30] In contrast, our results indicate epileptic seizures as a negative predictor for both early and late functional outcome.

The highest rate of early or acute-symptomatic seizures is within 24 hours after injury, and an overall increased risk for seizures and epilepsy prevails for decades.[9,34] The occurrence of early seizures is an additional risk factor for late seizures leading to the diagnosis of epilepsy.[35] Up to 86% of patients develop further seizures within 2 years.[25] Temkin et al[30] showed a significant reduction of early epileptic seizures (14% vs. 4%, RR 0.25) by using phenytoin as a prophylactic antiepileptic treatment. Over time, new antiepileptic drugs were introduced into the market and were compared with the formal gold standard phenytoin.[30] In patients with TBI and also in those with aSDH, levetiracetam showed a similar efficacy of seizure reduction with a significantly lower adverse effect profile compared with phenytoin.[35-38] In our study, >90% of patients who had seizures received levetiracetam as an antiepileptic treatment, which was well tolerated by our patients. However, to date, there is insufficient evidence of data to recommend the replacement of the former AED, so at the present time the use of levetiracetam instead of phenytoin depends on individual clinical decisions and may vary by national guidelines.[38] The most intriguing findings of our study were the identification of independent risk factors for epileptic seizures by performing multivariate logistic regression analysis: GCS 24 hours after operation (GCS ≤8), timing of operation ≥24 hours, and anticoagulation. These results were used for the development of the GATE-24 score system. Among those parameters, GCS was the most significant parameter. In patients with adequate consciousness (GCS 14 or 15), no prophylactic AED treatment is needed if the patient had no anticoagulation and the operation took place within 24 hours. In all other cases, prophylactic AED should be considered. Using the GATE-24 score, 96.4% of our patients with aSDH should be treated with a prophylactic antiepileptic treatment. In the future, the GATE-24 score would be a helpful guideline for the decision of prophylactic AED treatment in the clinical routine in ambivalent cases. On the basis of the prospective double-blind study examining prophylactic AED treatment in TBI patients, the American Academy of Neurology and BTF guidelines recommend 1 week for the duration of the prophylactic AED treatment because after 1 week, no significant difference in terms of outcome was detected between those groups.[11,12] Following the recommendation, we would suggest prophylactic antiepileptic treatment for the first week after aSDH in case of GATE-24 score <24.

Our study has some limitations. First, the present study is a retrospective analysis, which is subject to bias of unmeasured factors. Additionally, some patients had to be excluded due to insufficient data, which could lead to selection bias. Second, the EEG recordings were not consistently performed in all patients. We have a low threshold in performing EEG, especially in unconscious patients or in suspected epileptic seizures; however, this may lead to underestimation of the "real" incidence of epileptic seizures. Third, the number of patients was not large enough to achieve high sensitivity of the GATE-24 score. Fourth, patients with aSDH and seizures received mainly levetiracetam as an antiepileptic treatment, but we did not explicitly differentiate between different antiepileptic treatments.

CONCLUSION

Epileptic seizures are a common complication in patients with aSDH. However, the rates, predictors, and relevance of prophylactic antiepileptic treatment have been significantly understudied compared with chronic SDH. We observed epileptic seizures in 38% of patients with aSDH; after surgical treatment, about 90% of patients with preoperative seizures were seizure free. Independent predictors of epileptic seizures were a low GCS 24 hours after operation, delayed timing of operation (>24 hours), and anticoagulation. By integrating the predictors in a score system, a new guideline (GATE-24 score) was developed to ease the clinical decision of prophylactic antiepileptic treatment. Patients with epileptic seizures had an unfavorable functional outcome significantly more often and were associated with a significantly higher mortality rate. Thus there is hope to prevent seizures and subsequently improve the outcome of patients by using prophylactic antiepileptic treatment dependent on the GATE-24 score. Still, further prospective studies are warranted to verify the effect and benefit.

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Clinical Relevance of Seizure in Pediatric Patients with Isolated Acute Subdural Hematoma without Parenchymal Brain Injury

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Abstract

Purpose Isolated acute subdural hematoma (aSDH) in pediatric patients is rare, but it has a major impact on outcome. The purpose of this study was to determine incidence, seizure risk factors, and the outcome of pediatric patients with aSDH.

Methods Within a 10-year period (2007–2016), 10 children with aSDH were identified. Baseline characteristics and these parameters were analyzed: pediatric Glasgow Coma Scale (pGCS) score at admission and 24 hours after the operation, hematoma volume/side, and midline shift. Functional outcome was assessed at 3-month follow-up using the King's Outcome Scale for Childhood Head Injury score.

Results Three subgroups were identified depending on age and etiology: birth-associated, nontraumatic, and traumatic aSDH. The overall incidence of seizures was 60%, and an even higher rate (75%) was observed in children < 1 month of age. Of those patients, two (67%) developed late seizures. Significant predictors for seizures were low pGCS score at admission ($p = 0.03$) and 24 hours after surgery ($p = 0.03$) as well as increased midline shift ($p = 0.02$). Patients with seizures tended to have an unfavorable outcome.

Conclusion Pediatric patients with aSDH are at high risk for seizures, particularly if the pGCS score is low at admission/24 hours after the operation and midline shows a shift. Determining seizure-prone pediatric patients may facilitate early antiepileptic treatment and promote better clinical outcomes.

Keywords
- acute subdural hematoma
- seizure
- incidence
- risk factors
- pediatric

Introduction

Children are known to have a higher risk for seizures compared with adults.[1] Traumatic brain injury (TBI), in particular, is one of the major reasons for the development of posttraumatic seizures and was shown to be associated with poor functional and social outcome with a remission rate of only 47% in a long-time follow-up.[2–4] Among TBI, children with subdural hematoma (SDH) have a notably high incidence of seizures (36–89%) depending on the etiology, which is highly relevant due to the association with intellectual development and social intergration.[5,6] Therefore it is of great importance to identify seizure-prone patients and begin antiepileptic treatment as early as possible.

Several studies previously reported some risk factors for seizures in pediatric patients with a TBI-like mechanism of injury, particularly abusive head trauma, younger age (< 2 years), acute subdural hematoma (aSDH), and severity of trauma.[2,7,8] However, to date, studies describing the risk

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factors of seizures specifically in pediatric patients with isolated aSDH are rare. To the best of our knowledge, there is only one retrospective study reporting low birth weight and gestational age as risk factors for seizures in pediatric patients < 2 years of age with aSDH.[6] However, the focus was solely on those parameters without integrating other relevant predictors. Therefore we aimed to determine incidence and general risk factors of seizures in pediatric patients with isolated aSDH. Furthermore, functional outcome was assessed at follow-up.

Material and Method

Patients and Methods

The study was approved by the Clinical Ethics Committee of the Goethe-University of Frankfurt (No. 509/15). For this study, formal consent was not required. Using an electronic database, all patients < 18 years of age with an isolated aSDH admitted to our institution between January 2007 and December 2016 were identified. Inclusion criteria required aSDH as a primary diagnosis. Patients with traumatic parenchymal brain injury, other intracranial hemorrhage, or partially treated in another hospital were excluded.

A retrospective analysis was performed focusing on the risk factors for seizures. Patients were assigned to a seizure group based on the presence of a clinical manifestation of seizure, ictal patterns on electroencephalography (EEG), or a clinical suspicion of seizure with interictal epileptiform discharges at 1 week after onset (i.e., early posttraumatic seizures). At least one EEG diagnostic was performed during the clinical course. For the detection of late posttraumatic seizures, all patients were observed clinically after 3 months. In a case of clinical suspicion, an EEG was performed as well.

The following parameters were assessed in this study: age, sex, birth weight, gestational age, etiology, hematoma side/volume, midline shift, pediatric Glasgow Coma Scale (pGCS) score; eye opening: spontaneous (4) to no response (1); best verbal response: coos and babbles (5) to no response (1); best motor response: moves spontaneously and purposefully (6) to no response (1) at admission, pGCS score 24 hours after operation, surgical treatment, preoperative/postoperative seizures, rebleeding, antiepileptic medication, and outcome 3months after ictus.[9] In all patients, the EEG diagnostic was performed and evaluated by an EEG-certified neurologist.

Radiologic measurement was performed by examining the magnetic resonance imaging or computed tomography scans. Hematoma volume was measured by the ABC/2 formula.[10] In case of both-sided hematoma, the volumes were added together. For assessment of midline shift, the diameter was measured at the level of the greatest biparietal diameter. Functional outcome was evaluated by using the King's Outcome Scale for Childhood Head Injury (KOSCHI) at 3-month follow-up (1, death; 2, vegetative; 3, severe disability; 4, moderate disability; and 5, good recovery).[9]

Statistical Analysis

GraphPad Prism v.6.0 (GraphPad Software Inc., La Jolla, California, United States) was used for statistical analysis. Data were analyzed between group differences using the Mann-Whitney *U* test. For categorical variables, the Fisher exact test was used. Values are expressed as mean plus or minus the standard deviation. A $p \leq 0.05$ was defined as statistically significant.

Results

Age Distribution and Etiology of Acute Subdural Hematoma

►**Fig. 1** shows the age distribution and etiology of patients with aSDH. Thirteen patients < 18 years of age with

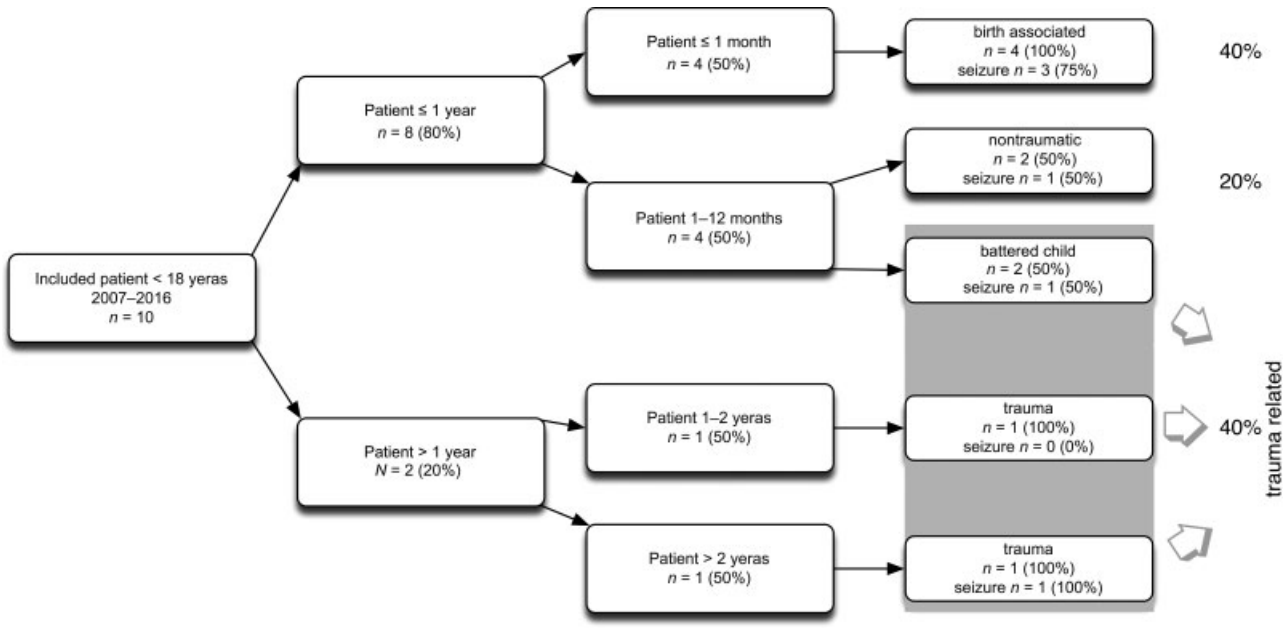

Fig. 1 Flowchart summarizing age and etiology distribution of the pediatric patients with acute subdural hematoma between 2007 and 2016.

isolated aSDH were identified from 2007 to 2016. In total, 10 patients with aSDH met the inclusion criteria; the other three patients were excluded due to the combined parenchymal brain injury. Eight of the patients (80%) were < 12 months of age, among them four patients (50%) under < 1 month. Two patients were > 1 year of age (20%), among them one patient > 2 years of age (50%). In all four patients < 1 month of age, the aSDHs were birth associated, whereas two of four children between 1 month and 1 year of age had "nontraumatic" bleeding of unknown etiology (50%), and in the other two a battered child syndrome (50%) was diagnosed. In children > 1 year of age, aSDH was associated with trauma.

Incidence and Risk Factors of Seizures

Overall, seizures were seen in 6 of 10 children (60%). Within the seizure group, 4 of 6 children (40%) had preoperative seizures, 4 (40%) had postoperative seizures, and 2 children (20%) had both pre- and postoperative seizures. The highest incidence of seizures was detected in children < 1 month of age (3 of 4 [75%]). Among those three children, two (67%) developed late posttraumatic seizures. None of them received prophylactic antiepileptic treatment.

►**Table 1** lists the predictors for seizures or epileptiform discharges. Low pGCS score at admission ($p = 0.03$), low pGCS score 24 hours after the operation ($p = 0.03$), and degree of midline shift ($p = 0.02$) were associated with the occurrence

Table 1 Baseline characteristic, incidence, and risk factors for seizures in pediatric patients[a]

Variable	*N* (%)	Seizure or epileptiform discharge (%)	No seizure or epileptiform discharge (%)	*p* Value
No. of patients	10	6 (60)	4 (40)	
Age, y ± SD	10 (100)	2.92 ± 6.9	0.5 ± 0.48	NS
Birthweight, g ± SD	7 (70)	3.388 ± 698.7	2.875 ± 176.78	NS
Gestational age, wk ± SD	7 (70)	38.4 ± 1.95	37.3 ± 2.08	NS
Battered child	2 (20)	1 (16.7)	1 (25)	NS
Timing of operation, d ± SD	10 (100)	2.5 ± 3.7	9.25 ± 9.95	NS
Sex (female)	4 (40)	2 (33.3)	2 (50)	NS
Trauma	4 (40)	2 (33.3)	2 (50)	NS
Hematoma side	10 (100)			
-Left	3 (30)	1 (16.7)	2 (50)	NS
-Right	3 (30)	3 (50)	0 (0)	NS
-Both	4 (40)	2 (33.3)	2 (50)	NS
Mean SDH volume, cm^3 ± SD	10 (100)	43.94 ± 33.11	45.6 ± 37.51	NS
Mean midline shift, mm ± SD	10 (100)	8.42 ± 3.88	1.67 ± 2.89	0.02
pGCS at admission, mean ± SD	10 (100)	8.57 ± 4.76	14.75 ± 0.5	0.03
pGCS 24 h postoperative, mean ± SD	10 (100)	7.33 ± 4.93	14.25 ± 0.96	0.03
Operation	8 (80)			NS
-Craniotomy/Craniectomy	4 (40)	3 (50)	1 (25)	
-Bore hole	4 (40)	1 (16.7)	3 (75)	
Conservative	2 (20)	2 (33.3)	0 (0)	
Preoperative seizure	4 (40)	4 (66.7)	0 (0)	NR
Postoperative seizure	4 (40)	3 (50)	1 (25)	NR
Patient with preoperative seizure preoperative seizure	2 (20)	2 (33.3)	0 (0)	
-Craniotomy	1 (10)			
-Burr hole	1 (10)			
Patient without preoperative seizure	2 (20)	1(16.7)	1 (25)	
Rebleeding	1 (10)	1 (16.7)	0 (0)	NS
KOSCHI, mean ± SD	9 (90)	3.83 ± 0.98	4.67 ± 0.58	NS

Abbreviations: KOSCHI, King's Outcome Scale for Childhood Head Injury; NS, not significant; pGCS, pediatric Glasgow Coma Score; SD, standard deviation; SDH, subdural hematoma; NR, not relevant for predictor analysis.
[a]Functional outcome was assessed via KOSCHI score at 3-month follow-up.

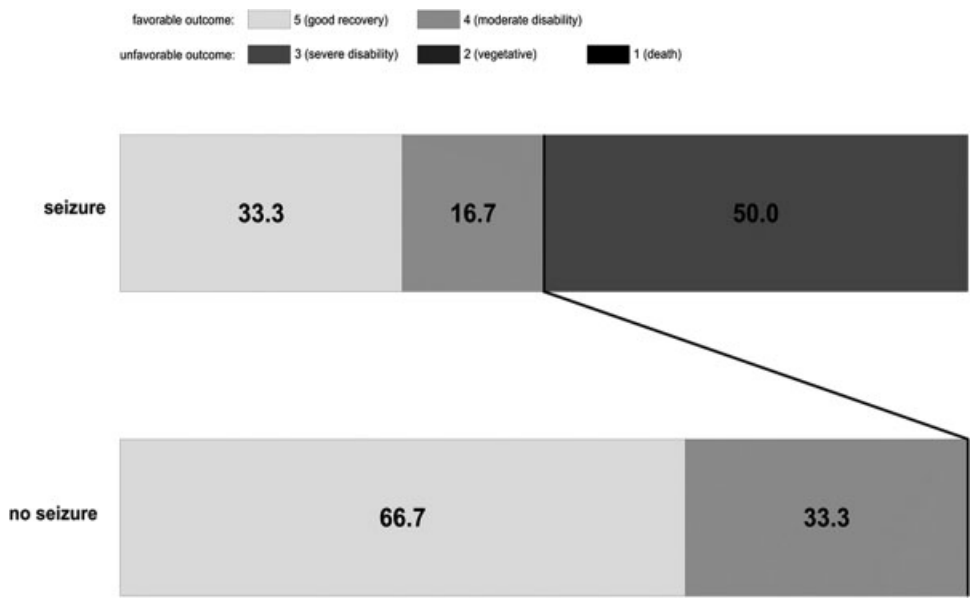

Fig. 2 Functional outcome at 3-month follow-up in seizure- and no-seizure group according to the King's Outcome Scale for Childhood Head Injury (KOSCHI). KOSCHI scores 4 and 5 are defined as a favorable outcome.

of seizures in patients with aSDH. In particular, pGCS score ≤ 14 at admission as well as 24 hours after surgery were significant cutoff predictors for seizures. Therefore age, sex, birth weight, gestational age, timing of the operation, hematoma volume or side, reoperation, and even the reoccurrence of bleeding were not significant. All patients in the seizure group received phenobarbital for anticonvulsive treatment, and under the treatment all patients were seizure free during the hospital stay. Afterward all patients received phenobarbital at least for a further 4 weeks. Among them, three of the six patients (50%) had developed late posttraumatic epilepsy at the 3-month follow-up.

We defined favorable outcome as KOSCHI score 4 and 5. Favorable outcome at 3-month follow-up was achieved in all four patients without seizures (100%), whereas in the seizure group, only three patients (50%) had a favorable outcome at follow-up (►**Fig. 2**). There was a trend toward favorable outcome in patients without seizures; however, no significance was reached.

Discussion

This present study analyzed isolated aSDH in a small series of children, focusing on the etiology of aSDH and the incidence and risk factors for seizures. Several large studies on aSDHs in adults have addressed this question, but in contrast to adults, aSDHs are rare in children. At this point the question arises whether risk factors in children will be similar to the larger adult series. In our series the etiology of aSDH was shown to depend on age: children < 1 month of age showed that the aSDHs were primary birth associated, whereas in older patients, traumatic injury was the most frequent cause. Twenty percent of the children were classified as "spontaneous" nontraumatic etiology because no other cause or no major trauma was reported by the parents. However, it is noteworthy that between 1 month to 1 year of age, children are learning to crawl, which could result in mild traumata that were not obvious and remained undetected as a trigger for aSDH. In addition, the possibility for an undetected battered child syndrome should not be disregarded. Indeed, trauma is considered as the most common cause for aSDH.[11] Abusive head trauma is discussed as one of the main reasons for traumatic injury in children < 3 years and accounts for 64% of all head injuries in children.[12]

In a multicenter study, Feldman et al analyzed children with an abusive head trauma and found that 89% of them had SDH, and among them 63% had aSDH and 20% a combined acute and chronic SDH.[12] Despite the low numbers of patients, we had similar results having two patients with aSDH due to abusive head trauma among traumatic injuries (50%), who were both < 2 years of age. In addition to trauma, the literature reported a high incidence of birth-related SDH in asymptomatic neonates between 9% and 46% after normal or instrumental delivery. Interestingly, most of the SDHs showed complete resolution after 1-month follow-up without intervention.[13] In our series, 25% of birth-related aSDHs corroborated these results. Rare causes for aSDH are coagulation disorder, infection, vascular malformation, and cancer.[11,13–15]

The overall incidence of seizures was 60% in aSDH; however, 80% of these children were < 1 year of age, 75% were neonates (< 1 month of age); thus the age of seizure onset seems to be of importance. Nardou et al reported a high incidence rate of seizures in the neonatal period of 1.8 to 3.5 per 1,000 live births.[1] Compared with the adults, the incidence of seizures is immensely high in pediatric patients.[8,16,17] Arndt et al examined seizures in pediatric patients clinically and with EEG and found that 77% of pediatric patients had posttraumatic seizures or epileptiform discharges, whereas 7% had subclinical seizures.[2,7] Similar high rates of epileptiform discharges on EEG (87% of patients) were found in adults previously, but in contrast to the results of EEG diagnostics, the incidence of clinical manifest seizures was low (24%).[8,18]

These results show a discrepancy between epileptiform discharges and clinical seizures in adults and pediatric patients. Indeed, some studies reported that seizures occur three times more commonly in pediatric patients than in adults.[19,20] This might be due to the different physiologic properties between the developing immature brain and the adult brain. Two possible mechanisms are discussed. First, γ-aminobutyric acid, as a major inhibitor, causes a paradoxical excitatory action due to the high Cl^- concentration in immature neurons.[1] Second, the neuronal architecture, connectivity, and supporting glia cells are not fully developed in the immature brain leading to a low threshold for seizures compared with the adult brain.[1] Subsequently, the enhanced intrinsic excitability of the immature brain is a risk factor for seizures; in other words, pediatric patients with a triggering factor like aSDH are prone to have seizures compared with adult patients.

To date, the pathophysiology of posttraumatic seizures in pediatric patients is not fully understood. It is postulated that early posttraumatic seizures would be triggered by acute neuronal damages, neurotransmitter excitatory and disturbance in ionic flux, whereas the late posttraumatic epileptic seizures would be triggered by structural changes, modified neurotransmitter functions, and gliosis.[2,8] It is well known that aSDH itself is a strong risk factor for seizures in pediatric patients as well as in adults.[3,21] Because pediatric patients are more susceptible to seizures than adults, we tried to identify risk factors for epileptic seizures in pediatric patients. The predictors in our study were low pGCS score at admission, low pGCS score 24 hours after surgery, and midline shift.

In a systematic review of pediatric patients with TBI, the strongest risk factor for seizures was severe trauma defined by GCS scores 3 to 8.[2,7] These findings were also presented in several other studies examining adult patients.[16,17,21–23] In our case, a GCS score ≤ 14 was already a significant risk factor for seizures. That implicates even a mild trauma as an indicator for the occurrence of seizures because pediatric patients are more vulnerable compared with adult patients. In terms of midline shift, contrary results were presented previously. Haltiner et al[24] examined risk factors for late posttraumatic seizures and found that midline shift > 5 mm was a significant predictor, whereas other studies did not show any significance.[18] It is speculated that the compressive effects of the hematoma might cause functional disarrangement of the contralateral or mesial cerebral hemisphere resulting in neuron excitability.[18]

However, in several studies, the volume of the SDH was not a significant predictor for seizures, so the pathophysiology still remains unclear.[21–23] Despite the widely analyzed risk factors for seizures in pediatric patients with traumatic injuries, just one study examined the risk factors for seizures in pediatric patients with isolated aSDH.[6] In contrast to our study, there were different risk factors determined such as low birth weight, low birth weight ratio, and early gestational age.[6] The difference might be due to a different selection of patients as compared with ours. In our database, 40% of the patients were < 1 month of age compared with 5% in the study of Kurabe et al.[6] Additionally, in our study 50% of the pediatric patients < 1 year of age had battered child syndrome whose pathophysiology is different than usual head trauma. Furthermore, it is hard to equalize and compare both studies because several parameters including pGCS score 24 hours after the operation or midline shift were not mentioned in the other study.

In 80% of the pediatric patients, surgical procedures were performed, and most of the patients recovered well after the operation. One patient of eight had rebleeding after burr hole trepanation that was successfully treated surgically. In general, surgical procedures were safe and efficient. In terms of outcome, 67% of pediatric patients had a favorable outcome after 3 months without any mortality. Compared with the high mortality rate of 22 to 60% in adult patients with aSDH, the results of our study are promising.[8,25] However, due to the small number of patients, an analysis for predictors of outcome could not be performed.

In our study, patients with seizures had a tendency toward poor functional outcome compared with patients without seizures. Several studies previously reported the association between seizures and poor functional outcome and higher mortality.[2,3,19,26,27] Even subclinical seizures were significantly associated with prolonged hospital stay and a poor functional outcome.[3,7,20] In the case of seizures, the standard treatment would be the use of antiepileptic drugs, but to date the role of prophylactic antiepileptic treatment is not clearly defined. In a double-blind study by Mandal et al, the prophylactic antiepileptic treatment in pediatric patients was not beneficial in reducing the occurrence of seizures. However, it should be noted that most of the pediatric patients were > 3 years of age, the incidence of seizures was lower than previously reported, and no differentiation between patients at high and low risk was made.

In contrast, Temkin et al reported a significant reduction of seizures by using prophylactic antiepileptic drugs in patients with TBIs.[28] Thus it is still ambiguous if a prophylactic antiepileptic treatment should be recommended or not in pediatric patients with aSDH. It might be important to recognize seizure-prone pediatric patients with aSDH to assess the probability of seizure occurrence before using prophylactic antiepileptic treatment. Additionally, because the incidence of seizures is very high in infants, further studies are warranted for the use of prophylactic antiepileptic treatment in infants in the future.

Some limitations of our study should be mentioned. First, we had a small number of patients not representing all cohorts of pediatric patients. However, the incidence of seizures as well as the distribution rate of each parameter were similar to the other studies with larger numbers of patients, indicating the relevance of our study. But we observed only pediatric patients with isolated aSDH. Despite the expected statistical low power due to small numbers, we had significant predictors for seizures that should alert all clinicians to these predictive factors. In the future a larger multicenter audit may help address this limitation. Second, we used the ABC/2 technique for SDH volume calculation that is validated for intracerebral hematoma.[10] Therefore absolute values might be not exact; however, it is sufficient

for relative comparison between the values. Third, the present study is a retrospective analysis and therefore subject to bias of unmeasured factors.

Conclusion

In the present study, we analyzed seizures in children with isolated aSDH. The overall incidence of seizures was 60%. The rate was even higher in children $<$ 1 month of age (up to 75%). Significant predictors for epileptic seizures were low pGCS score at admission (pGCS score $\leq$14), 24 hours after surgery (pGCS score $\leq$14), and midline shift. Because the threshold between epileptiform discharge and clinical manifested epileptic seizures is lower than in adults, it might be beneficial to perform regular EEG diagnostics in all pediatric patients with aSDH, even in the case of mild trauma. It is important to remember that seizures are associated with a poor functional outcome. Therefore seizure-prone pediatric patients should be recognized, and a prophylactic antiepileptic treatment may be considered individually. However, further prospective-based studies are needed to verify the effect of prophylactic antiepileptic treatments to build a standardized guideline for high-risk pediatric patients.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this article.

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ORIGINAL ARTICLE

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Seizure and status epilepticus in chronic subdural hematoma

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Background: Acute symptomatic seizure (ASz) and status epilepticus (SE) are serious conditions associated with poor quality of life, with unfavorable psychosocial and functional outcome. Chronic subdural hematoma (cSDH) is a common neurosurgical disease related to those complications; therefore, we aimed to evaluate incidence, predictors of ASz/SE, and outcome in this cohort.

Methods: We retrospectively analyzed patient diagnosed cSDH between 2010 and 2017. Beside their incidence of ASz/SE, patient characteristics, symptoms at admission, comorbidities, and all previously published relevant parameters were assessed. Recurrence rate and functional outcome were analyzed at hospital discharge and 90-day follow-up.

Results: A total of 375 patients were included; incidence of ASz was 15.2% and of SE, 1.9%. In the univariate analysis, drainage insertion ($P = 0.004$; OR = 0.3) was a significant negative predictor for ASz/SE and multivariate analysis, including all significant parameters, designated GCS ≤13 at admission ($P = 0.09$; OR = 1.9), remote stroke ($P = 0.009$; OR = 2.9), and recurrence rate within 14 days ($P = 0.001$; OR = 3.3; with an incidence of 13%) as independent predictors for ASz/SE. Overall, patients with ASz/SE had significantly unfavorable outcome at discharge (54.7%; $P < 0.001$) and follow-up (39.5%; $P < 0.001$) with only slight improvement. Late seizures occurred in 3.8% within follow-up period. Any patient with SE had an unfavorable outcome at discharge without any improvement at follow-up having a mortality rate of 14.2%.

Conclusion: Independent predictors for ASz/SE are GCS ≤13 at admission, remote stroke, and recurrent hematoma in patients with cSDH, which is associated with worse functional outcome, particularly those with SE. Due to the higher rate of seizures than recurrence rate, a routine pre- and postoperative EEG besides CT is recommended.

KEYWORDS
chronic subdural hematoma, EEG, functional outcome, predictors, seizures, status epilepticus

1 | INTRODUCTION

Seizures are common, serious sequelae of traumatic brain injury (TBI) occurring up to 20 years after initial injury.[1] According to the recommendation of the International League Against Epilepsy (ILAE), they can be classified into three categories: immediate (within 24 hours after acute brain insult), early (within 7 days) and late seizure (after 7 days), the latter being indicative of high seizure recurrence rate leading to diagnosis of epilepsy.[2-4] Immediate and early seizures are considered as acute symptomatic and may also present as status epilepticus (SE).[5] Several studies have identified risk factors for occurrence of acute symptomatic seizure (ASz), such as older age, alcoholism, art of trauma, depressed skull fracture, dura penetration, penetration injuries and cortical injuries. In particular, acute (aSDH) and chronic subdural hematoma (cSDH) have been shown to be one of the major predictors for ASz and a high cumulative probability of 27.8% for late seizures occurring within 2 years. [6-12]

Previously, we were able to show a strong correlation between occurrence of seizures and aSDH, which was well in line with previous studies, whereas opinions regarding seizures and cSDH are contradictory.[11,13,14] The reported incidence of seizures in cSDH varies in between 2% and 42%, and some predictors, such as alcoholism, male sex, low Glasgow Coma Scale (GCS) at admission, previous stroke, and hematoma density, were identified in a smaller number of patients. However, various selected parameters with insufficient differentiation between ASz and late seizures made it impossible for a meta-analysis, leaving the main conclusion elusive.[9,14-23] Furthermore, the significance of status epilepticus (SE) in cSDH, which is associated with even higher morbidity and mortality, is not well studied.[24,25] Indeed, there are further questions remaining as to with which prognosis and perspective we should be alerted and treat the patients with cSDH-associated ASz. Since the incidence, as well as related costs of cSDHis increasing nationwide due to aging demographic alteration, the relevance of cSDH and the management of its complications are prominent and will become increasingly so, wherefore it is important to gain a closer insight into this field.[26,27]

The purpose of this investigation was to analyze ASz and SE in individuals with cSDH, stratify independent predictors by applying all relevant reported parameters from the previously published systematic review, and to evaluate outcome at discharge as well as at follow-up of 90 days.

2 | METHODS

2.1 | Ethical approval and data availability

The study was approved by the local ethical committee (EK 509/15). No informed consent of patient was required for this study. All data generated or analyzed during this study are included in this published article.

2.2 | Study population and data collection

This single-center retrospective study included 401 consecutive patients admitted with chronic subdural hematoma between January 2010 and December 2017. Inclusion criteria were age over 18 years with a cSDH diagnosed by a CT or MRI scan. Patients with

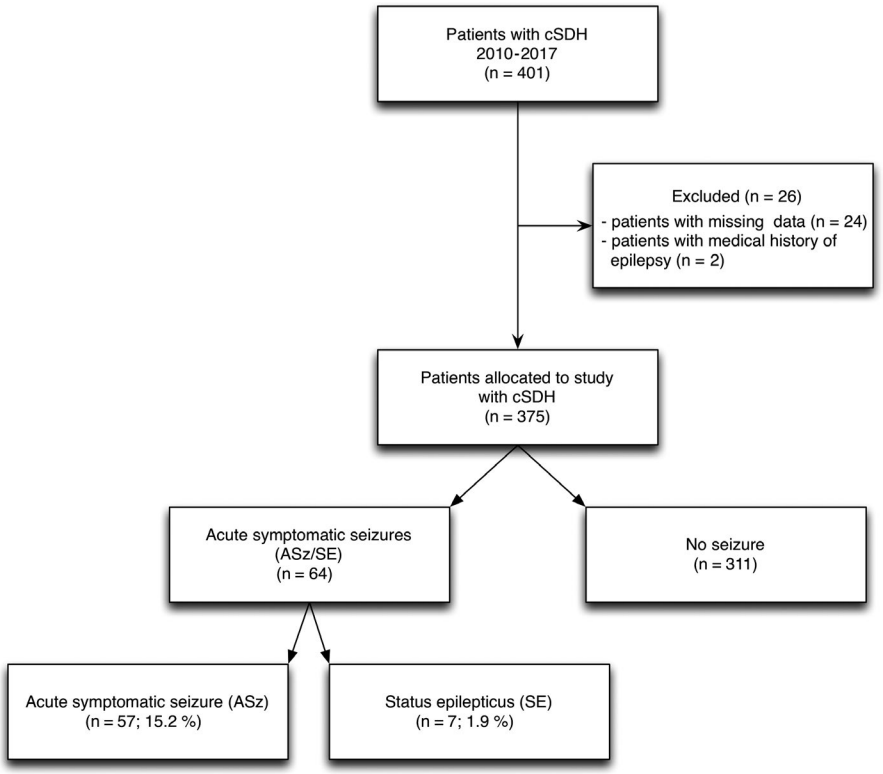

FIGURE 1 Flowchart summarizing the enrollment, allocation, and analysis of patients with chronic subdural hematoma admitted to author's institution between 2010 and 2017

insufficient clinical/radiological data, combined contusion injury of brain parenchyma, combined intracerebral/subarachnoidal hemorrhage or medical history of epilepsy with antiepileptic treatment were excluded (Figure 1).

Chronic subdural hematoma was defined as a SDH surrounded by hematoma membrane and consisting of dark liquefied blood at operation. Moreover, CT or MRI was performed in symptomatic patients or in patients after TBI and either hypodense (-intense) to isodense (-intense) hematoma was defined as cSDH as well.

We included all potential risk factors reported in a recently published systematic review of seizures in subdural hematoma.[14] The following parameters were assessed:

Patient age; sex; symptoms at admission; GCS at admission (summation of scores for eye, verbal, and motor responses); alcohol abusus, use of anticoagulation; art of treatment; radiological parameters, such as hematoma size, density, and volume; midline shift; postoperative trapped air in the CT scan; and SDH recurrence within 14 days and 90 days. In addition, the comorbidities of each patient were assessed and defined as follows: hypertension; atrial fibrillation; diabetes mellitus; cardiovascular disease; respiratory disease; renal disease; dementia; metabolic disease; haematological disease; malignant tumor; remote stroke; pneumonia; and urinary tract infection.

For volumetric measurement, a previously published ABC/2 formula was used by evaluating preoperative CT or MRI scan.[28] Midline shift was measured at the level of pineal gland and was calculated in case of unilateral cSDH. Density of each cSDH was classified into three categories: hypodense, isodense, and mixed dense, depending on the Hounsfield unit difference compared with the brain parenchyma. Surgical treatment was indicated if the patient had clinical symptoms like headache, vomiting, hemiparesis, gait disturbance on the basis on radiological proven cSDH. In case of asymptomatic patient, we performed radiological follow-up CT scan in 2 weeks and if there was a progress of hematoma detected, additional surgical indication was possibly made. All patients were initially planned for a burr hole trepanation with subdural blake-drainage insertion. In case of an immediate brain expansion, subdural drainage insertion was waived. In case of recognized thick membrane and mixed blood component, we decided for a small craniotomy to relieve the SDH. In all patients, at least one postoperative CT scan was performed within 3 days and at follow-up within 90 days. If serial CT scans within 90 days revealed increased subdural collection compared with the CT findings postoperatively, and if preoperative clinical symptoms persisted or recurred, a recurrence of cSDH was diagnosed. Asymptomatic reaccumulation of hematoma was considered as nonsurgical and conservative treatment was performed. Thus, the need for a reoperation was defined as recurrence of cSDH. None of the patients received prophylactic antiepileptic treatment as it is not recommended in the german guidelines.[29]

The primary functional outcome was assessed by modified Rankin scale (mRS) at hospital discharge, dichotomized as favorable (mRS 0-2) and unfavorable (mRS 3-6) outcomes. The secondary outcome was assessed by mRS at 90-day follow-up after hospital discharge.

2.3 | Definition of acute symptomatic seizure, status epilepticus, and late seizure

Acute symptomatic seizure (ASz) was defined as recommended by the ILAE, either as documented clinical seizure manifestation, ictal pattern in the EEG recordings, or clinical suspicion with interictal epileptiform discharges in the EEG recordings in close temporal relationship with acute brain insult.[4] Close temporal relationship was defined as within 1 week of initial clinical diagnosis of cSDH or recurrence of hematoma.

Status epilepticus was clinically defined as generalized tonic-clonic seizure lasting for more than 5 minutes or complex-partial seizures lasting for more than 10 minutes, according to the latest ILAE definition and used in previous studies on SE in our department.[30,31] Both ASz and SE were abstracted into a general category of "acute symptomatic seizures or status epilepticus" (ASz/SE).

Occurrence of late seizures was defined after 1 week after the clinical diagnosis of cSDH without an associated hematoma recurrence or any other acute brain injury.

2.4 | Study design

Patients were divided into two groups: the ASz/SE group and no seizure group. For the subgroup analysis, the ASz/SE group was further divided into two subgroups: the ASz group and the SE group. The aim of the study was to evaluate incidence, predictors, and impact on outcome in patients with cSDH-associated ASz and SE. In case of predictor analysis, separate analysis of SE was not reasonable due to the small number of patients; therefore, we analyzed it for ASz/SE in general. In addition, we provided the mortality and occurrence of late seizures at 90-day follow-up.

2.5 | Statistical analysis

IBM SPSS Statistics (version 22; IBM Corp.) was used for data analysis. Data were described using means ± standard deviations and numbers of patients, including percentages for continuous and categorical variables. Univariate and multivariate linear regression analyses were performed to obtain independent predictors for the ASz as well as the SE group. For parametric parameters, an unpaired *t* test was used. For nonparametric parameters, variables were analyzed in a contingency table using either Fisher's exact test or chi-squared test, as appropriate. To assess the impact of the variables, odds ratios with 95% confidence intervals were calculated. A *P*-value ≤0.05 was considered as statistically significant and all tests were 2-tailed.

3 | RESULTS

3.1 | Basic characteristics

Among 401 patients with cSDH admitted to our center, 375 patients (93.5%) were included in this study. Twenty-six patients had to be excluded due to missing clinical or radiological data and medical

TABLE 1 Predictors for acute symptomatic seizure and status epilepticus in patients with chronic subdural hematoma

		Acute symptomatic seizures (%)			
	Total (%)	Seizure	Status epilepticus	No seizure (%)	*P*-value[a]
Basic characteristics					
Patient number (n)	375	57 (15.2)	7 (1.9)	311 (82.9)	
Age ≥75 (y)	188 (50.1)	30 (52.6)	4 (57.1)	154 (49.5)	0.60
Female	127 (33.9)	18 (31.6)	4 (57.1)	105 (33.8)	0.93
Symptoms at admission					
Headache	96 (25.5)	21 (28.4)	1 (14.3)	75 (24.8)	0.54
Confusion	32 (8.5)	7 (12.3)	0 (0)	25 (8.0)	0.45
Reduced consciousness	48 (12.8)	6 (10.5)	2 (28.6)	40 (12.9)	0.94
Nausea	47 (12.5)	2 (3.5)	2 (28.6)	43 (13.8)	0.1
Paresis	109 (29.1)	15 (26.3)	3 (42.9)	91 (29.3)	0.86
Paresthesia	10 (2.7)	0 (0)	2 (28.6)	8 (2.6)	0.80
Gait impairment	140 (37.3)	19 (33.3)	1 (14.3)	120 (38.6)	0.27
Speech disorder	77 (20.5)	15 (26.3)	1 (14.3)	61 (19.6)	0.33
Syncope	4 (1.1)	0 (0)	0 (0)	4 (1.3)	0.36
Visual disorder	4 (1.1)	0 (0)	0 (0)	4 (1.3)	0.36
Incontinence	17 (4.5)	5 (8.8)	0 (0)	12 (3.9)	0.17
None	16 (4.3)	0 (0)	0 (0)	16 (5.1)	0.06
GCS at admission					
GCS 3-13	71 (18.9)	16 (28.1)	4 (57.1)	51 (16.4)	**0.006**
GCS 14-15	304 (81.1)	41 (71.9)	3 (42.9)	260 (83.6)	**0.006**
Comorbidities					
Hypertension	240 (64.0)	34 (59.6)	7 (100)	199 (64.0)	0.99
Atrial fibrillation	60 (16.0)	11 (19.3)	2 (28.6)	47 (15.1)	0.39
Diabetes mellitus	74 (19.7)	10 (17.5)	3 (42.9)	61 (19.6)	0.90
Cardiovascular disease	57 (15.2)	7 (12.3)	1 (14.3)	49 (15.8)	0.51
Respiratory disease	24 (6.4)	5 (8.8)	1 (14.3)	18 (5.8)	0.29
Renal disease	39 (10.4)	8 (14.0)	1 (14.3)	30 (9.6)	0.29
Dementia	40 (10.7)	8 (14.0)	1 (14.3)	31 (10.0)	0.33
Metabolic disease	130 (34.7)	20 (35.1)	3 (42.9)	107 (34.4)	0.82
Hematologic disease	37 (9.9)	6 (10.5)	1 (14.3)	30 (9.6)	0.75
Malignant tumor	28 (7.5)	5 (8.8)	0 (0)	23 (7.4)	0.91
Remote stroke	35 (9.3)	11 (19.3)	1 (14.3)	23 (7.4)	**0.004**
Pneumonia	12 (3.2)	1 (1.8)	2 (28.6)	9 (2.9)	0.46
Urinary tract infection	15 (4.0)	4 (7.0)	1 (14.3)	10 (3.2)	0.09
Alcohol abusus	6 (1.6)	0 (0)	0 (0)	6 (1.9)	0.39
Anticoagulation	179 (47.5)	31 (54.4)	3 (42.9)	145 (46.6)	0.41
Radiological parameters					
Unilateral	264 (70.3)	39 (68.4)	5 (71.4)	220 (70.7)	0.75
Right sided	121 (32.3)	16 (28.1)	2 (28.6)	103 (33.1)	0.47
left sided	143 (38.0)	23 (40.4)	3 (42.9)	117 (37.6)	0.67
Bilateral	111 (29.7)	18 (31.6)	2 (28.6)	91 (29.3)	0.76
Density					
Hypodense	91 (24.1)	23 (31.0)	3 (42.9)	58 (19.1)	0.08
Isodense	124 (32.9)	17 (23.0)	1 (14.3)	107 (35.3)	0.08

(Continues)

TABLE 1 (Continued)

	Total (%)	Acute symptomatic seizures (%)		No seizure (%)	*P*-value[a]
		Seizure	Status epilepticus		
Mixed dense	161 (42.9)	25 (49.1)	3 (42.9)	133 (42.8)	0.89
Volume (cm^3 ± SD)	133.6 ± 70.3	128.6 ± 63.4	143.8 ± 81.6	134.3 ± 71.5	0.68
Midline shift (mm ± SD) (unilateral cSDH)	8.1 ± 4.6	7.3 ± 4.1	5.0 ± 3.9	8.3 ± 4.7	0.19
Treatment					
Operation					
Burr hole	341 (90.9)	54 (94.7)	7 (100)	280 (90.0)	0.23
Craniotomy	7 (1.9)	1 (1.8)	0 (0)	6 (1.9)	1.0
Drainage insertion	323 (86.1)	45 (78.9)	7 (100)	271 (87.1)	**0.004**
Conservative	27 (7.2)	2 (3.5)	0 (0)	25 (8.0)	0.17
Postoperative course					
Trapped air in CT scan	273 (72.8)	42 (73.7)	6 (85.7)	225 (72.3)	0.66
Recurrence within 14 d	49 (13.1)	15 (26.3)	3 (42.9)	31 (10.0	**<0.001**
Recurrence within 90 d	63 (16.8)	15 (26.3)	1 (14.3)	47 (15.1)	0.07

[a]Chi-square test. Bold values are significant values (p<0.05).

history on seizures. Table 1 shows the basic characteristics in detail. Median age was 75 (interquartile range of 67.4-81.9), ranging from 26 to 104 years. The sex ratio was 2:1 with 248 (66.1%) men and 127 (33.9%) women. Above all, 62 patients (16.5%) had a traumatic injury, whereas other patients did not remember of a trauma with unclear etiology of cSDH. Most frequent symptoms at admission were gait impairment (37.3%), paresis (29.1%), and headache (25.5%), followed by speech disorder, reduced level of consciousness, nausea, incontinence, confusion, paresthesia, and syncope. In 16 patients (4.2%), there were no symptoms at all counting as incidental detection, 327 patients (87.2%) had at least one comorbidity, and 35 patients (9.3%) had more than five comorbidities. Two hundred and 64 patients had unilateral hematoma (70.3%), right and left sided nearly equally distributed, while the rest of the patients had bilateral cSDHs (29.7%). In over 90%, surgical treatment was performed and, in most of the cases (86.2%), drainage was inserted. Postoperatively, recurrence rate of cSDH within 14 days was 13% and 16% within 90 days from hospital discharge. None of the patients received seizure prophylaxis in this study.

3.2 | Incidence and predictors of ASz and SE

Acute symptomatic seizure/status epilepticus occurred in 64 of 375 patients, resulting in an incidence of 17.1%. All patients with ASz/SE received at least one antiepileptic treatment. Mostly, levetiracetam (86%) was used as primary antiepileptic drug. Of 375 patients, no patient received prophylactic antiepileptic treatment. In the subgroup analysis, the incidence of ASz was 15.2% and of SE, 1.9% (Figure 1). In over 90% of those patients, antiepileptic treatment was started, most commonly with levetiracetam (90%).

In the univariate analysis, predictors for ASz/SE were GCS ≤13 at admission (OR = 2.3, 95% CI [1.3-4.3]), remote stroke (OR = 2.9, 95% CI [1.4-6.2]), and hematoma recurrence within 14 days (OR = 3.5, 95% CI [1.8-6.8]). Drainage insertion (OR = 0.3, 95% CI [0.1-0.7]) was a negative predictor, suggesting a beneficial effect. There was a clear negative trend toward no symptoms at admission (OR = 0.1, 95% CI [0.0-0.7]), wherefore we included this parameter in the multivariate analysis as well.

In the multivariate analysis, independent predictors for ASz/SE were GCS ≤13 (OR = 1.9, 95% CI [1.0-3.6]), remote stroke (OR = 2.9, 95% CI [1.3-6.4]), and hematoma recurrence within 14 days (OR = 3.3, 95% CI [1.6-6.5]). Interestingly, hematoma volumes, midline shift, surgical treatment strategy, and trapped air in the postoperative CT scan were not significant predictors.

3.3 | Functional outcome at hospital discharge and 90-day follow-up

Overall, favorable outcome at discharge was achieved in 254 patients (67.7%) and the mortality rate was 1.6%. Regarding 90-day follow-up, 238 patients (63.5%) were eligible for analysis. There was a significant improvement of functional outcome in 83.2% ($P < 0.001$) with a low mortality rate of 2.5% at 90-day follow-up.

Comparing ASz/SE and no seizure group, ASz/SE more frequently had an unfavorable outcome at hospital discharge (mRS 3-6: 54.7% vs 27.7%, $P < 0.001$; 2.5 ± 1.7 vs 1.5 ± 1.5; $P < 0.001$; Figure 2A). Similar results were reflected in the subgroup analysis with ASz and SE group (Figure 2B). Particularly comparing between ASz and SE group, the SE group had significantly worse outcome with an unfavorable outcome rate of 100% (mRS 3-6: 100% vs 49.2%, $P < 0.001$; 4.4 ± 0.8 vs 2.3 ± 1.7, $P = 0.002$).

At 90-day follow-up, there was no difference compared to the previous results. Despite the overall higher frequency of a favorable outcome in ASz/SE group, there was still a significant gap compared

with the no seizure group (mRS 0-2:60% vs 86.5%, $P < 0.001$; 1.5 ± 1.6 vs 0.9 ± 1.4, $P = 0.02$; Figure 3A). In the subgroup analysis, patients with SE significantly more frequently had an unfavorable outcome without any improvement at follow-up (mRS 3-6:100% vs 25.8%, $P < 0.001$; 4 ± 1.4 vs 1.4 ± 1.4, $P < 0.001$ Figure 3B). The mortality rate of the SE group was 4.4-fold higher compared with the ASz group and 7.1-fold higher compared with no seizure group, establishing SE as a strong negative outcome predictor in cSDH patients.

At 90-day follow-up, nine patients developed late seizures, an overall incidence of 3.8%. Six of these patients had ASz/SE prior to late seizures, resulting in a risk rate of 15.8%, whereas among the no seizure group, the risk rate of late seizures was only 1.5%.

4 | DISCUSSION

Due to aging demographic alteration and cSDH as a disease of mostly older patient, it is increasingly common neurosurgical condition with which we are confronted in our daily practice.[32] However, there remains uncertainty regarding the relevance of acute symptomatic seizures in outcome prediction and management of patients with, leading to missing consensus (eg, drainage insertion or not).[33,34] In brief, we conducted this study with additional SE analysis to gain new insight and perspective into cSDH-associated complications.

Previously, the overall incidence of seizures in patients with cSDH was reported between 2% and 42% and ASz between 1% and 23%, depending on the use of EEG diagnostics, treatment, the grade of severity, and status of patients.[9,14-23] In the literature, it is not well distinguished between ASz and late seizures in cSDH, leading to some mixture of the incidence and prevalence data.[14,16-23] However, concerning that, presumably, most of the studies dealt with acute symptomatic seizures, we observed a similar incidence of ASz/SE of 17%. Moreover, Seifi et al presented epidemiological data reporting initially an SE incidence of 0.5% in SDH patients with increasing rates over the course of the study. The authors described the possibility of initial underdiagnosis of SE due to low

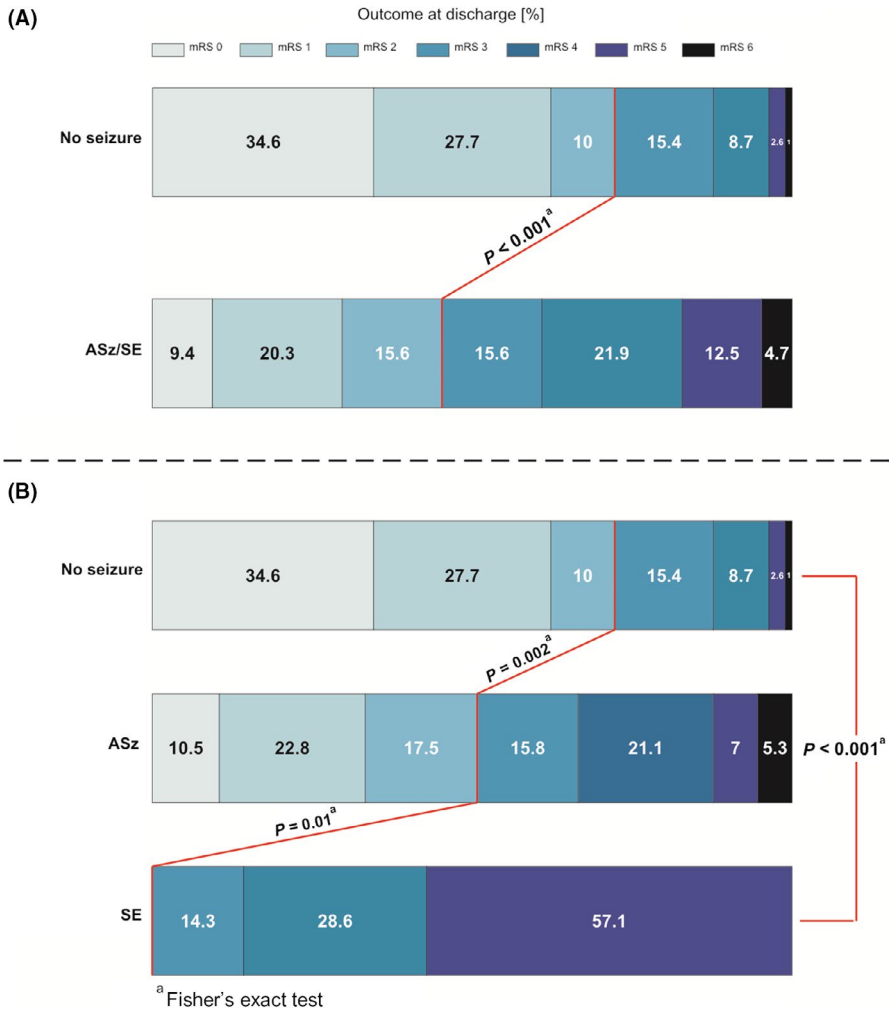

FIGURE 2 A, Outcome assessed via modified Rankin scale (mRS) in chronic subdural hematoma with acute symptomatic seizures (ASz/SE) and no seizure at hospital discharge. Favorable outcome was defined as mRS 0-2, and unfavorable outcome was defined as mRS 3-6. B, Subgroup analysis of outcome assessed via mRS in patients with acute symptomatic seizure (ASz) and status epilepticus (SE)

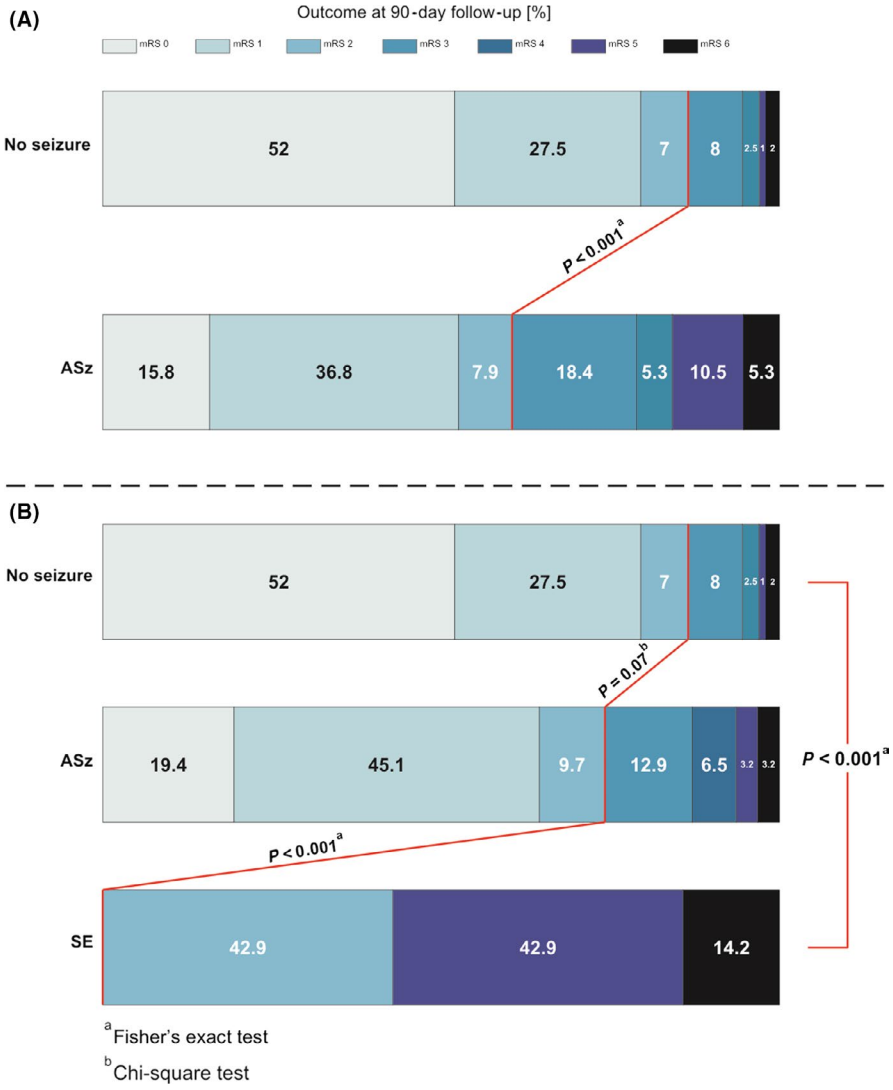

FIGURE 3 A, Outcome assessed via mRS in patients with ASz/SE and no seizure at 90-d follow-up. B, Subgroup analysis of outcome assessed via mRS in patients with ASz and SE

index of suspicion.[24] As expected, we observed a higher rate of SE of 2% in our study.

Three independent predictors for ASz/SE were identified: GCS ≤13 at admission, remote stroke, and recurrence of hematoma within 14 days. On the one hand, it is well-established that one of the main risk factor for seizures is the severity of trauma expressed by GCS.[1,6,7,14,29] Independent from the underlying disease, such as brain contusion, acute SDH, traumatic SAH, or skull fractures, Herman et al reported 2.7-fold high-risk ratio in moderate and 17-fold high-risk ratio for ASz in severe TBI elevated for 2 years.[1,5] In addition, the severity of trauma was not restricted to the prediction of ASz, but was also a major predictor for late seizures and development of post-traumatic epilepsy. Englander et al reported a rate of 17%-24% of late seizures in patients with moderate-to-severe TBI within 2 years, and several others studies reported the occurrence of ASz as an additional predictor for recurrent late seizures, resulting in posttraumatic epilepsy risk of up to 80% in this group.[5-7] On the other hand, the etiology of cSDH underlies often in a mild trauma and the low GCS might be a result of chronic or subclinical seizures that were unrecognized prior to surgery. Whereas cCT are recommended in AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) and Brain Trauma Foundation (BTF) guidelines extensively and done more than once, an EEG control is still not recommended as a standard procedure.[35-37] According to our data, we would recommend two routine diagnostic concepts: EEG diagnostic prior to surgery and after surgery in patients with risk factors (low GCS, remote stroke). Hence, unnecessary surgery might be waived and antiepileptic treatment might be adequately started in order to anticipate late seizures.

Interestingly, drainage insertion was shown to negatively associate with ASz/SE occurrence in the univariate analysis, but not in the multivariate analysis, while we had expected the opposite result considering a potential mechanical irritation of cortex via drainage. This finding might be simply due to the facts that (a) the hematoma recurrence rate is reduced by drainage insertion as shown in previous studies; and (b) hematoma recurrence itself was an independent predictor for ASz/SE.[33,34,38] Further, drainage could reduce the rest hematoma and its blood metabolite resulting in a less irritation of cortex. Moreover, the hemoglobin with the blood compounds and its degradation products are known to be highly epileptogenic due

to its irritation of the cortical surface.[7] In case of beginning recurrent hematoma by capillary leakage, fresh erythrocytes mixed by those degradation products might be an additional irritating factor for cortical surface in low-threshold situation resulting in clinical manifestation of epileptic seizure. Therefore, our results suggest that drainage insertion maybe one of the important steps in surgical treatment of cSDH not only to prevent hematoma recurrence but also the development of ASz/SE (Table 2).[33]

To date, there are only few case reports and few studies analyzing SE in patients with SDH.[15,24,39-41] The commonality of those studies was the association of worse outcome with SE, which we also observed in our study. Particularly, there was no improvement of outcome in the course at all, indicating a devastating perspective of this complication. To identify predictors for SE, Seifi et al reported major organ dysfunction correlating to the diagnosis of SE (with only seven patients); however, we could not observe a direct correlation between comorbidities and SE.[24] Nonetheless, we should focus on this rare entity, because outcome was dismal (0% favorable outcome). Further, in the last decades, there have been several studies focusing on short- and long-term outcome in patients with TBI-associated seizures.[42-44] In summary, ASz, as well as late seizures, is associated with unfavorable outcome regarding physical, cognitive, and psychosocial reintegration up to 5 years after initial injury and is an independent predictor for unfavorable outcome as well.[42,43] We could reproduce those findings in our study, particularly regarding cSDH. Surely, there are other factors having influence on outcome, whereas the sole-limiting factor in our study was the significant higher presence of remote stroke in patients with seizure compared to control group whereas other comorbidities were similar between those groups. SE and late seizures resulting in diagnosis of epilepsy are usually subject to antiepileptic drug (AED) treatment, while such antiepileptic treatment of single ASz remains debatable. Indeed, there are some retrospective studies reporting contradictory results regarding the prevention of seizures in cSDH, but a prospective randomized trial is missing for clarification.[9,15,16,18,45] Formerly, Temkin et al showed a double-blind fashion significant reduction of ASz in patients with TBI using phenytoin for 6 months as a prophylactic AED; however, they failed to show the reduction of late seizures.[46] Nowadays, new AED, such as levetiracetam, has been developed and prospective studies have shown the similar effect of seizure reduction with favorable safety profile and better long-term outcome.[47-49] Since ASz is significant predictors for the development of posttraumatic epilepsy, we think that a prophylactic treatment with new AED might be beneficial in selected cohorts of patients. At least, if some of the predictors for ASz/SE are present in patients with cSDH, a prophylactic AED might be considered in the clinical practice, especially due to the high rate of ASz/SE until discharge (17%).

4.1 | Study limitations

There are some limitations in the present study that should be addressed. This study was a retrospective study with its bias of unmeasured factors. This could have been aggravated through the exclusion of some patients, insufficient medical record according to alcohol abusus, and loss of follow-up. On the other hand, patients lost to follow-up had comparable characteristics and outcome at discharge, which might reduce the bias. Furthermore, EEG diagnostic was not consistently performed in all patients and very few had continuous EEG monitoring, which may lead to underestimation of seizure and missing of subclinical seizures. So, a systematic identification of ASz and further a standardized treatment should be warranted. This may be an interesting topic for the future to analyze subclinical seizure via long-term EEG recordings.

5 | CONCLUSION

ASz and SE are common, serious clinical manifestations in cSDH with an incidence of 15% and 2%, respectively. The rate is similarly high as the SDH recurrence rate with 13% during clinical course or 16% until 90 days FU. Independent predictors for ASz/SE were GCS ≤13 at admission, remote stroke, and recurrence of cSDH within 14 days.

TABLE 2 Independent predictors for acute symptomatic seizure/status epilepticus in the uni-/multivariate analysis

	Univariate analysis			Multivariate analysis		
	P-value	OR	CI 95%	*P*-value	OR	CI 95%
Symptoms at admission						
None	0.06	0.1	0.0-0.7	1.0		
GCS at admission						
GCS 3-13	0.006	2.3	1.3-4.3	0.04	1.9	1.0-3.6
Comorbidities						
Remote stroke	0.004	2.9	1.4-6.2	0.009	2.9	1.3-6.4
Operation						
Drainage insertion	0.004	0.3	0.1-0.7	0.51		
Postoperative course						
Recurrence within 14 d	<0.001	3.5	1.8-6.8	0.001	3.3	1.6-6.5

Furthermore, drainage insertion is a negative predictor of ASz/SE, likely due to the prevention of recurrent hemorrhage. The identification of high-risk patients is important, because ASz and SE are associated with the development of epilepsy and inherits unfavorable outcome at discharge as well as at follow-up. Thus, we recommend pre- and postoperative monitoring not only by cCT but also by EEG in perspective for a prophylactic antiepileptic treatment.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Sae-Yeon Won involved in study concept and design, and acquired analyzed, and interpreted the data. Daniel Dubinski designed the study and acquired the data. Lisa Sautter acquired the data and analyzed the data. Elke Hattingen, Volker Seifert, and Felix Rosenow involved in critical revision of manuscript for intellectual content and study supervision. Thomas Freiman designed the study and critically revised the manuscript for intellectual content. Adam Strzelcyzk designed the study, analyzed and interpreted the data, and critically revised the manuscript for intellectual content. Juergen Konczalla designed the design, analyzed and interpreted the data, critically revised the manuscript for intellectual content, and supervised the study.

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Supervised Valsalva Maneuver after Burr Hole Evacuation of Chronic Subdural Hematomas: A Prospective Cohort Study

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Abstract

Research on chronic subdural hematoma (cSDH) management has primarily focused on potential recurrence after surgical evacuation. Herein, we present a novel postoperative/non-invasive treatment that includes a supervised Valsalva maneuver (SVM), which may serve to reduce SDH recurrence. Accordingly, the aims of the study were to investigate the effects of SVM on SDH recurrence rates and functional outcomes. A prospective study was conducted from December 2016 until December 2019 at the Goethe University Hospital Frankfurt. Of the 204 adult patients with surgically treated cSDH who had subdural drains placed, 94 patients were assigned to the SVM group and 82 patients were assigned to the control group. The SVM was performed by having patients blow into a self-made SVM device at least two times/h for 12 h/day. The primary end-point was SDH recurrence rate, while secondary outcomes were morbidity and functional outcomes at 3 months of follow-up. SDH recurrence was observed in 16 of 94 patients (17%) in the SVM group, which was a significant reduction as compared with the control group, which had 24 of 82 patients (29.3%; $p = 0.05$) develop recurrent SDHs. Further, the infection rate (e.g., pneumonia) was significantly lower in the SVM group (1.1%) than in the control group (13.4%; $p < 0.001$; odds ratio [OR] 0.1). At the 3-month follow-up, 85 of 94 patients (90.4%) achieved favorable outcomes in the SVM group compared with 62 of 82 patients (75.6%) in the control group ($p = 0.008$; OR 3.0). Independent predictors for favorable outcome at follow-up were age (OR 0.9) and infection (OR 0.2). SVM appears to be safe and effective in the post-operative management of cSDHs, reducing both recurrence rates and infections after surgical evacuation, thereby resulting in favorable outcomes at follow-up.

Keywords: chronic subdural hematoma; functional outcome; predictors; recurrence; recurrent hematoma; supervised Valsalva maneuver

Introduction

Chronic subdural hematomas (cSDH) are a common neurosurgical disorder that continues to increase in incidence in part because of an aging population and the prevalence of anticoagulant regimens.[1,2] Although cSDH are well known in neurosurgery, there is a lack of class I evidence, which complicates treatment decisions thereby resulting in inter-clinical discrepancies with regard to both surgical and post-operative management.[3]

The standard treatment of cSDH involves surgical evacuation in cases that are not able to be managed conservatively. Weigel and coworkers summarized three principal techniques – twist drill craniotomy, burr hole trepanation and craniotomy – and reported that burr hole trepanation appeared to be the most effective treatment option given a lower morbidity of 3.8% and rate of recurrence of 12.1%.[4] Therefore, burr hole trepanation is performed most frequently worldwide for the treatment of cSDHs.[4–7] Further work has gone on to confirm that subdural drain insertion significantly reduces rates of recurrence.[5] Current evidence has also demonstrated the utility of placing a subperiosteal drain, which results in even lower recurrence rates.[8]

It is of note that recurrence rates after the initial treatment of cSDH range between 5% and 30%.[5,9,10] Recently, Edlmann and coworkers reported on 26 randomized controlled trials in cSDH covering medical treatment with steroids, tranexamic acid, different surgical techniques, and middle meningeal artery embolization.[11] Notably, there is a dearth of studies examining post-operative management, which may also influence recurrence rates.

Interestingly, one of the predictors related to the recurrence of SDH is post-operative hematoma volume, which may perpetuate a chronic inflammatory process.[9,12,13] Accordingly, one of the main goals of cSDH treatment must be the maximum evacuation of the hematoma. In line with such thinking, a supervised Valsalva

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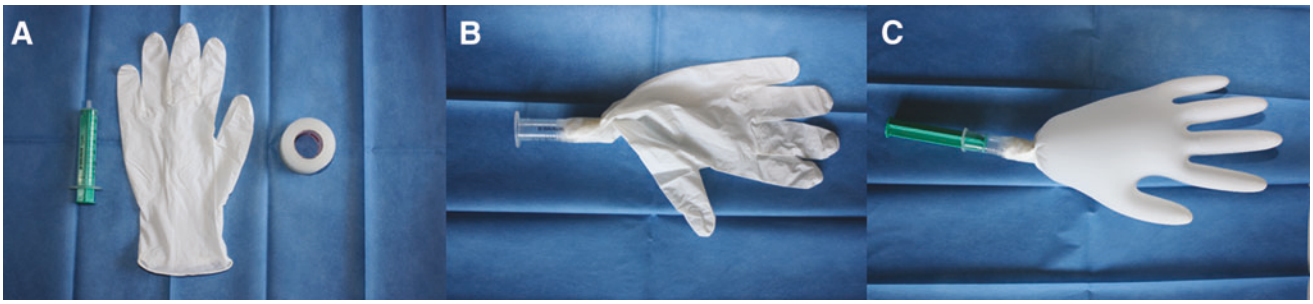

FIG. 1. **(A)** Materials: 10 mL syringe (Injekt®, B. Braun Melsungen AG, Melsungen, Hessen, Germany), one medium-size glove (B. Braun Melsungen AG, Melsungen, Hessen, Germany) and Leucoplast® (BSN medical GmbH, Hamburg, Germany) **(B)** The glove is circled around the syringe and fixed by Leucoplast. **(C)** After blowing into the syringe, the glove should be in full tension. We defined this procedure as supervised Valsalva maneuver. Color image is available online.

maneuver (SVM) has been part of the post-operative management at the Goethe University Hospital Frankfurt for >20 years. The physiology driving the idea is centered on a desire to increase intracranial pressure and in so doing, provoke brain expansion, thereby promoting drainage of blood product(s).

Herein, our aim was to formally analyze the effects of post-operative SVM-centered management on the recurrence rates of cSDH after burr hole evacuation in an effort to standardize the most appropriate/effective methods of post-operative management.

Methods

Standard protocol approvals, registrations, and patient consents

The study is registered at clinicaltrials.gov. One exception to report is that we performed a prospective comparative cohort study. The institutional review board at each site approved the study. Written informed consent was obtained according to the Declaration of Helsinki. Patients unable to give consent were excluded from the study. The study is registered at clinicaltrials.gov. (NCT04060186).

Study Design

Via a prospective cohort study, all patients presenting with cSDH who were surgically treated between December 2016 and December 2019 were included within the study. Patients with acute SDH, subacute SDH, acute-on-chronic SDH, unable to give consent, and/or in whom a subdural drain had not been placed were excluded from the study. Further, we excluded all patients with Glasgow Coma Scale (GCS) <15 after operation to rule out selection bias between the interventional and control arms. By doing so, both groups were well matched.

Procedures

At time of admission, the neurosurgeon on call determined clinical status, pertinent medical history, and the use of anticoagulants/antiplatelet agents. Thereafter, all patients included in the study underwent surgery during which a single burr hole (14 mm in maximum diameter) was placed overlying the hematoma. The hematoma was subsequently washed out using lactated Ringer's solution as irrigation via a 10 mL syringe. Outer membranes were opened and inner membranes were opened in selected cases. Ultimately, a subdural drain was placed with a suction bulb, and the patients were transferred to the neurosurgical wards for monitoring/recovery.

After consent or assent, patients were divided into two groups in a non-randomized fashion: (1) an SVM group and (2) a control group.

Given that the Goethe University Hospital Frankfurt has two different wards, the assignment of each patient was ward dependent. As mentioned, patients who were post-operatively disoriented (GCS <15) were excluded because they were unable to perform an SVM adequately, which would result in a selection bias. Therefore, the study was performed in a ''semi-randomized'' fashion.

The instructions for SVM-device production are shown in Figure 1. All patients in the SVM group received one SVM device and were asked to blow into the syringe, resulting in inflation of the attached rubber glove. After reaching maximal tension of the glove, the patient stopped and the air was released. This maneuver was performed at least two times per h for 12 h/day for 2 days (Fig. 2). The patients were supervised by our study physicians and received stepwise instructions.

After surgery, one group performed SVM for 2 days as per the previously described protocol. The subdural drain was removed between post-operative days 1 and 3, at which point a post-

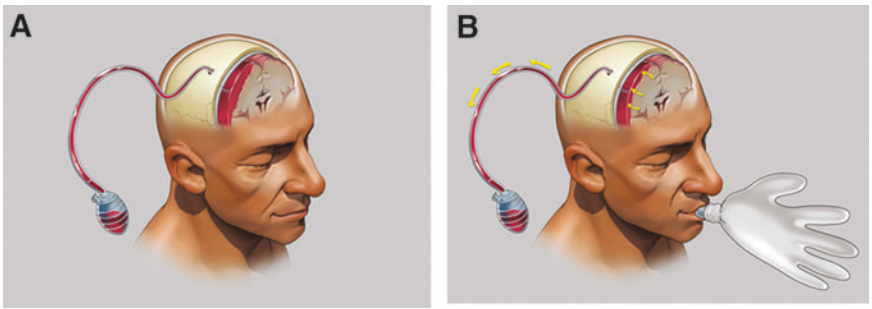

FIG. 2. **(A)** Surgical treatment and subdural drain insertion in patients with chronic subdural hematoma. **(B)** Supervised Valsalva maneuver after surgery resulting in an increase of intracranial pressure and brain expression with promoting higher flow rate of drainage. Color image is available online.

operative computed tomography (CT) scan was performed. Patients were subsequently discharged home or to a local rehabilitation center and followed for at least 3 months. At discharge as well as at follow-up, neurological outcomes were assessed via a modified Rankin Scale (mRS), and hematomas surveilled with CT scans. Volumetric measurement of the hematomas was conducted as has been previously defined.[14] Measurements of maximal deviation of the midline structures at the level of the foramen of Monroe were used to calculate midline shift.

The primary study outcome was the recurrence rate. Recurrent hematoma was defined as reoperation in patients with previously surgically treated cSDH via burr hole trepanation. Critically, surgeons assessing the need for reoperation were blinded to control or SVM treatment status of the initial cSDH. Secondary outcomes were morbidity and functional outcomes at 3 months of follow-up.

The data sets generated and/or analyzed during the current study are included in this article.

Statistical analysis

Chi-square test was used to compare categorical variables. Median and interquartile range (IQR) were calculated for numerical data. Normality was confirmed with the Kolmogorov–Smirnov test and in cases of normal distribution, a *t* test was employed. For data that did not fall into a normal distribution, the Mann–Whitney *U* test was applied.

We employed logistical regression to investigate the effects of SVM and other previously described independent variables on the following measures: recurrence rate and favorable outcome (mRS 0–2) at discharge and at follow-up. For all variables, odds ratios (OR) with 95% confidence interval (CI) were calculated. All tests were two sided; p values <0.05 were considered to be statistically significant in both the univariate and multivariate analysis.

Results

The overall study design is illustrated in Figure 3. A total of 272 patients with surgically treated cSDH were eligible, with 68 patients having been excluded from the final analysis (i.e., exclusion criteria vs. lost to follow-up), resulting in a total enrollment of 176 patients. Of these, 94 patients were assigned to the interventional SVM group and 82 patients were assigned to the control group. Patient characteristics are presented in Table 1; no clinical and radiological differences were noted among the SVM and controls groups (i.e., parameters including GCS at admission, comorbidities, hematoma

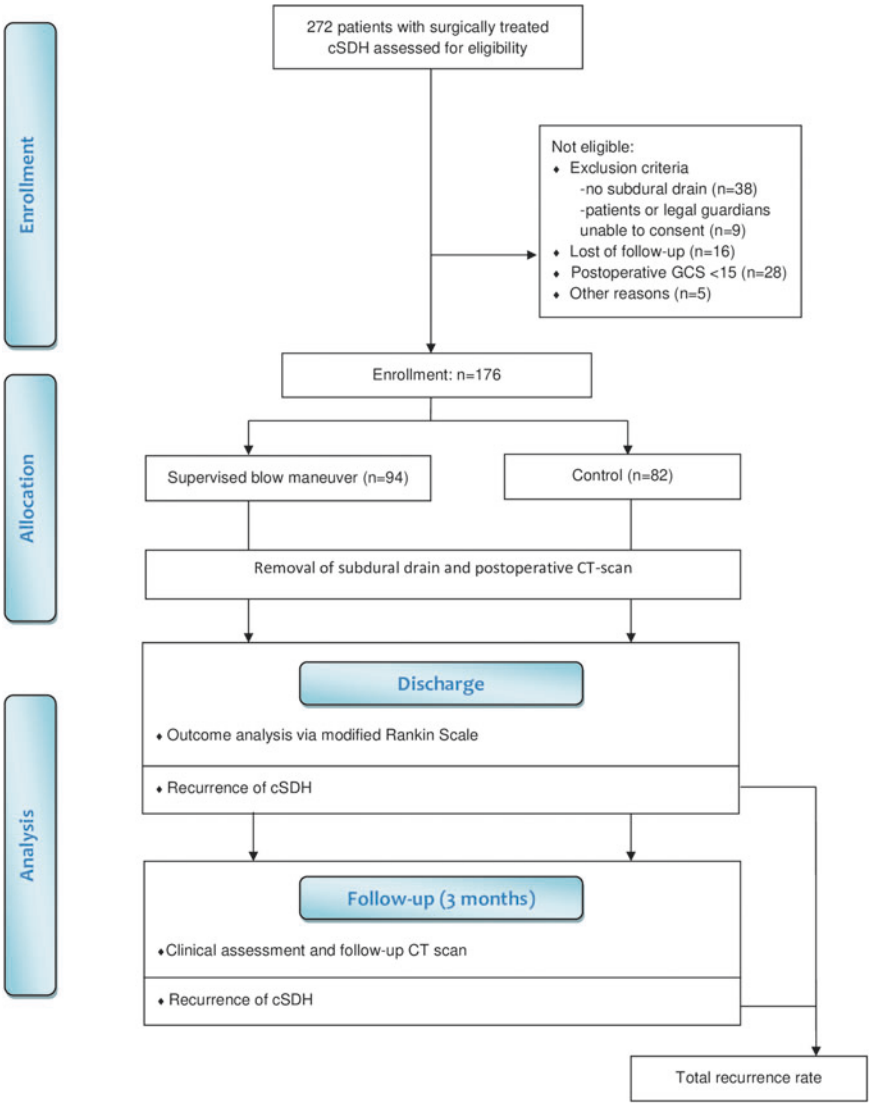

FIG. 3. Supervised Valsalva maneuver (SVM) study structure. Color image is available online.

Table 1. Patient Characteristics, Medical History, Admission Status and Surgical Treatment

	Supervised Valsalva maneuver	*Control*	p *value*
Number	94	82	
Age, median ± IQR (years)	75 (65-80)	74.5 (62-80)	0.49
Sex (female)	23 (24.5%)	27 (32.9%)	0.21
Medical history			
Hypertension	50 (53.2%)	50 (61%)	0.3
Diabetes mellitus type II	16 (17%)	22 (26.8%)	0.12
Atrial fibrillation	16 (17%)	15 (18.3%)	0.83
Cardiovascular disease	18 (19.1%)	20 (24.4%)	0.4
Coronary disease	16 (17%)	16 (19.5%)	0.67
Respiratory disease	12 (12.8%)	7 (8.5%)	0.37
Renal disease	7 (7.4%)	10 (12.2%)	0.29
Metabolic disease	31 (33%)	26 (31.7%)	0.86
Remote stroke/TIA	11 (11.7%)	5 (6.1%)	0.2
Hematological disease	7 (7.4%)	4 (4.9%)	0.48
Oncology	12 (12.8%)	9 (11%)	0.72
Drug history			
Anticoagulation or antiplatelet	46 (48.9%)	41 (50%)	0.89
GCS at admission			
13-15	86 (91.5%)	71 (86.6%)	0.3
7-12	8 (8.5%)	11 (13.4%)	0.3
3-6	0 (0%)	0 (0%)	1.0
CT			
Volume, median (IQR)	118.4 (81.3-154.1)	119 (66.3-152.7)	0.96
Midline shift, median (IQR)	6.6 (3.8-10.2)	6.6 (5.5-10.5)	0.58
Side			0.62
Left	33 (35.1%)	25 (30.5%)	
Right	34 (36.2%)	28 (34.1%)	
Both	27 (28.7%)	29 (35.4%)	
Density			
Hypodense	23 (24.5%)	12 (14.6%)	0.1
Isodense	36 (38.3%)	35 (42.7%)	0.51
Hyperdense	35 (37.2%)	35 (42.7%)	0.46
Operation			
Burr hole trepanation	94 (100%)	82 (100%)	1.0
Drain	94 (100%)	82 (100%)	1.0
<2days	2 (2.1%)	5 (6.1%)	0.18
=2days	85 (90.4%)	68 (82.9%)	0.14
>2days	7 (7.4%)	9 (11%)	0.42

Chi-square test was used for parametric statistical analysis. Mann–Whitney *U* test was used for non-parametric statistical analysis.
IQR, interquartile range; TIA, transient ischemic attack; GCS, Glasgow Coma Scale.

volume, midline shift, hematoma side or uni-/bilateral hematoma) resulting in a well matched pair. In the majority of cases, the duration of the subdural drain placement was 2 days (86.9%).

Symptoms upon admission are displayed in Table 2. The most common symptoms were headache (37.5%), followed by gait impairment (35.2%), hemiparesis (25%), speech arrest (20.5%), confusion (17%), nausea (14.2%), and impaired consciousness (9.1%). In eight patients (4.5%), the hematoma was diagnosed incidentally. The majority of patients had a total of two symptoms (37.5%), followed by one (27.3%), and three symptoms (23.3%), whereas four patients (2.3%) had five or more symptoms at admission.

The recurrence rate of hematomas was significantly lower in the SVM group than in the control group (17% vs. 29.3%; $p = 0.05$; OR 0.5 Cl 95% 0.2–1.0) at 3 month follow-up (Table 3). After adjusting for potentially confounding variables such as age, GCS at admission, neurological deficit (defined as the presence of paralysis, gait impairment, or aphasia), infection during the clinical course, and uni- or bilateral hematoma, a logistical regression analysis revealed SVM as the single significant parameter associated with a reduction in recurrence rate (OR 0.5 Cl 95% 0.2–1.0) (Table 4).

At discharge, favorable outcome was achieved in 137 patients (77.8%). Of these, 81 patients (86.2%) were in the SVM group and 56 patients (68.3%) were in the control group ($p = 0.004$; OR 2.9 Cl 95% 1.4–6.1). At 3 month follow-up, patients in the SVM group were significantly more likely to have reached favorable outcomes than patients in the control group ($p = 0.008$; OR 3.0 Cl 95% 1.3–7.1). The median length of hospital stay was 6 days (IQR 4–8) without significant difference between both groups. Via logistical regression analysis, there were several independent predictors shown to be associated with outcomes at discharge: age (OR 0.9 [0.9–1.0]), GCS at admission (OR 1.6 [1.2–2.3], and infection during hospitalization (OR 0.0 [0–0.3]). At follow-up, age (OR 0.9) and infection (OR 0.2) remained as independent predictors for favorable outcome.

With regard to patient safety/the non-invasive nature of the SVM intervention, it is prudent to highlight that there were no episodes of

Table 2. Symptoms at Admission of cSDH Patients

Headache	66 (37.5%)
Gait impairment	62 (35.2%)
Hemiparesis	44 (25%)
Speech arrest	36 (20.5%)
Confusion	30 (17%)
Vomiting	25 (14.2%)
Impaired conciousness	16 (9.1%)
Seizure	9 (5.1%)
Sensory deficit	9 (5.1%)
Syncope	5 (2.8%)
Incontinence	1 (0.6%)
Cumulative number of symptoms at admission	
Asymptomatic	8 (4.5%)
1 symptom	48 (27.3%)
2 symptoms	66 (37.5%)
3 symptoms	41 (23.3%)
4 symptoms	9 (5.1%)
≥ 5 symptoms	4 (2.3%)

cSDH, chronic subdural hematoma

syncope or hemodynamic instability noted throughout the course of our study. One intracerebral hematoma was detected in each group, whereas additional one epidural hematoma (1.2%) and one acute SDH (1.2%) requiring surgical treatment were diagnosed in the control group. Further, the infection rates were significant lower in the SVM interventional group (1.1%) than in the control group (13.4%) ($p < 0.001$; OR 0.1 [0.0–0.4]) (Table 3).

Discussion

This is the first study investigating the effects of SVM after surgical evacuation of cSDH. Here, we show that SVM proved to be an effective tool capable of reducing the recurrence rate of SDH as compared with controls. Further, patients in the SVM arm of our study had fewer infections and better neurological outcomes at follow-up than patients in the control group. No adverse effects related to SVM were detected during the course of our study, again highlighting the favorable safety profile of this non-invasive intervention.

Several studies have reported multiple predictors related to recurrence after evacuation of cSDH including age, large pre-operative hematoma volume, anticoagulation/platelet status, seizures, bilateral cSDH, radiological findings reflective of hematoma type (laminar type, different densities), and large post-operative residual hematoma.[9,10,15–17] In an effort to reduce the burden of recurrent hematomas, most studies thus far have investigated different surgical techniques, such as craniotomy or burr hole, number of burr holes, different positions of the burr holes (frontal or parietal), direction of drainage, subdural or subperiosteal drainage, intraoperative irrigation, and, in the case of irrigation, the question of fluid temperature.[4,8,18–20] In addition, medical treatments with agents such as dexamethasone or atorvastatin and endovascular interventions (i.e., middle meningeal artery occlusion) have recently been investigated as potential modalities for the reduction of SDH recurrence; such interventions aim to perturb the neuroinflammatory axis.[13,21,22] Post-operative residual hematoma has been demonstrated to trigger continuous inflammation via a litany of interleukins/chemokines and inflammatory cells.[13] Accordingly, surgical interventions and post-operative regimens should attempt to maximize evacuation of the hematoma. In line with such thinking, our SVM intervention was designed to facilitate the drainage of the residual hematoma via an intraoperatively placed subdural drain. A Valsalva maneuver, consisting of a voluntary expiratory effort against a closed airway, leads to an increase in intrathoracic and intra-abdominal pressure.[23] As a result, intracranial pressure increases and the residual hematoma is displaced from the subdural space via brain expansion.[24] (Fig. 2) It is of note that post-operative CT scans often reveal subdural air collections, which are also a risk factors for recurrence.[10,25] In our view, such patients with subdural air collection would also benefit from SVM, as this maneuver can reduce air pockets within the subdural cavity.

One concern associated with SVM was a possibility of hemodynamic instability, as it is known that such maneuvers may alter blood pressure/heart rate via the activation of baroreceptors.[23] Importantly, canonical teaching would suggest that patients may be at risk of re-bleeding, as SVM induces an increase in intracranial pressure. Despite such hypothetical risks, our study did not identify any cardiovascular complications and/or bleeding secondary to SVM.

Table 3. Primary and Secondary Outcome Analysis in Supervised Valsalva Maneuver and Control Group

	Supervised Valsalva maneuver	*Control*	p *value*	*OR (Cl 95%)*
Number of patients	94	82		
Recurrence within 3 months	16 (17%)	24 (29.3%)	0.05	0.5 (0.2-1.0)
Favorable outcome (mRS0-2)				
• At discharge	81 (86.2%)	56 (68.3%)	0.004	2.9 (1.4-6.1)
• At 3 months	85 (90.45)	62 (75.6%)	0.008	3.0 (1.3-7.1)
Mortality rate				
• At discharge	0 (0%)	0 (0%)	1.0	NA
• At 3 months	0 (0%)	1 (1.2%)	0.28	NA
Morbidity	2 (2.2%)	14 (17%)	<0.001	0.1 (0.0-0.4)
• Infection[a]	1 (1.1%)	11 (13.4%)	0.001	0.1 (0.0-0.6)
• Acute subdural hematoma	0 (0%)	1 (1.2%)	0.47	NA
• Epidural hematoma	0 (0%)	1 (1.2%)	0.47	NA
• Intracerebral hematoma	1 (1.1%)	1 (1.2%)	1.0	NA
Hospital stay, median (IQR)	6 (4-8)	5 (4-8)	0.96	NA

Fisher exact test and *t* test were used for primary and secondary outcome analysis.
[a]Infection includes pneumonia, urinary tract infection, and sepsis.
OR, odds ratio; Cl, confidence interval; mRS, modified Rankin Scale; IQR, interquartile range; NA, not applicable.

Table 4. Adjusted Logistical Regression Outcome Analysis by Variables with Potential Influence on the Relationship between Supervised Valsalva Maneuver and Recurrence/Outcome at Discharge as Well as at Follow-Up

	p *value*	*OR (Cl 95%)*
Recurrence rate		
Age	0.65	1.0 (1.0-1.0)
GCS at admission	0.61	1.1 (0.8-1.6)
Neurological deficit	0.23	1.6 (0.7-3.4)
Infection	0.86	1.1 (0.3-4.4)
Coagulopathy or anticoagulation/antiplatelet	0.19	1.6 (0.8-3.4)
Unilateral hematoma	0.21	0.7 (0.5-1.2)
Supervised Valsalva maneuver	0.05	0.5 (0.2-1.0)
Favorable outcome at discharge		
Age	0.001	0.9 (0.9-1.0)
GCS at admission	0.005	1.6 (1.2-2.3)
Neurological deficit	0.57	1.3 (0.5-3.1)
Infection	0.001	0.0 (0-0.3)
Coagulopathy or anticoagulation/antiplatelet	0.19	0.7 (0.3-1.7)
Unilateral hematoma	0.21	1.2 (0.7-2.1)
Supervised Valsalva maneuver	0.18	1.8 (0.8-4.2)
Favorable outcome at follow-up		
Age	0.002	0.9 (0.9-1.0)
GCS at admission	0.84	1.0 (0.7-1.5)
Neurological deficit	0.9	1.1 (0.4-2.7)
Infection	0.03	0.2 (0-0.8)
Coagulopathy or anticoagulation/antiplatelet	0.25	0.6 (0.2-1.5)
Unilateral hematoma	0.15	1.5 (0.9-2.7)
Supervised Valsalva maneuver	0.1	2.2 (0.9-5.5)

Neurological deficit was defined as paresis, gait impairment or aphasia at admission.

GCS, Glasgow Coma scale; OR, odds ratio; CI, confidence interval.

In contrast, there were additional benefits related to SVM such as lower rates of infection (e.g., pneumonia). This may in part be because SVM also has a positive effect on the lungs via the prevention of post-operative atelectasis. Boden and coworkers investigated the effect of physiotherapy/breathing exercises in a large cohort of patients after abdominal surgery and showed an absolute risk reduction of pulmonary complications, including pneumonia, in up to 15% of patients.[26] Further, it is known that respiratory physiotherapy and mobilization are key factors in improving functional status and reducing the sequalae of pneumonia.[27] In accordance with this the SVM group displayed significantly better outcome than the control group at discharge as well as at follow-up.

In our study, the recurrence rate of cSDH after initial treatment was 23.8%; 17% in the SVM group and 29.3% in the control group. A similar recurrence rate was reported in the recently published Randomized Trial of Follow-Up CT after Evacuation of Chronic Subdural Hematoma (TOSCAN) study (i.e., 23%).[28] In patients with bilateral cSDH, an even higher recurrence rate of 28.7% has been described.[29] On the other hand, other studies have reported lower rates of recurrence (i.e., between 9% and 18%).[7,8,17] As has been discussed in detail, several factors have been identified that play a role in the recurrence rates; however, an additional explanation for the high recurrence rate might be simply the fact that there is no common post-operative management strategy among several clinics. Some of them suggest regular radiological follow-up whereas others do not perform follow-up at all except in cases of clinical deterioration. In our study, we performed regular radiological follow-ups in all patients, which might be the simple explanation for the high recurrence rate, because clinical unapparent progressive recurrent hematoma was diagnosed as well.

To date, there are several studies investigating pre-operative and perioperative therapeutic regimes to reduce recurrence rate, yet the postoperative treatment of patients with cSDH is often overlooked. Based on this study, we believe that SVM might be a simple, effective, and safe post-operative treatment to reduce recurrent hematoma after surgical treatment of cSDH.

Limitations

This is a non-randomized study, which may have led to unintentional selection bias. However, as noted, the groups were well matched in clinical traits/presentation. We feel that it is also important to highlight a challenge that is often encountered in medicine, the need for individual effort, which is required to perform SVM. Clearly, some patients were more persistent about performing SVM, whereas others appeared less motivated; future work will seek to clarify how best to engage all parties in their care.

Conclusion

SVM appears to be safe and effective in the post-operative management of cSDHs, reducing both recurrence rates and infections after surgical evacuation, thereby resulting in favorable outcomes at follow-up. Given its reproducible and safety profile, such a non-invasive post-operative intervention may indeed have clinical utility in both high and low resource settings, and may positively impact the care of neurosurgical patients.

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available in the article and its supplementary materials.

Author Disclosure Statement

J.D.B has positions and equity in CITC Ltd. and Avidea Technologies, and is on the Scientific Board of Advisors for POCKiT Diagnostics. The other authors have nothing to disclose.

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