Fortschritte in der Therapie intrakranieller Blutungen – mehr als nur Blutdruckmonitoring?

Paul Muhle

KFO 342

Darlegung potentieller Interessenkonflikte

Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

Als Referent versichere ich, dass in Bezug auf den Inhalt des folgenden Vortrags keine Interessenskonflikte bestehen, die sich aus einem Beschäftigungsverhältnis, einer Beratertätigkeit oder Zuwendungen für Forschungsvorhaben, Vorträge oder andere Tätigkeiten ergeben.

Allgemeines

- Intrazerebrale Blutungen verursachen ca. 12% aller Schlaganfälle in Deutschland und ca. 9 – 27% aller Schlaganfälle weltweit

- Höhere Inzidenz bei älteren Menschen
  - steigende Prävalenz von Amyloidangiopathien
  - im Vgl. zu jüngeren schlechtere Einstellung des Blutdrucks
  - häufigerer Einsatz von Antikoagulanzien

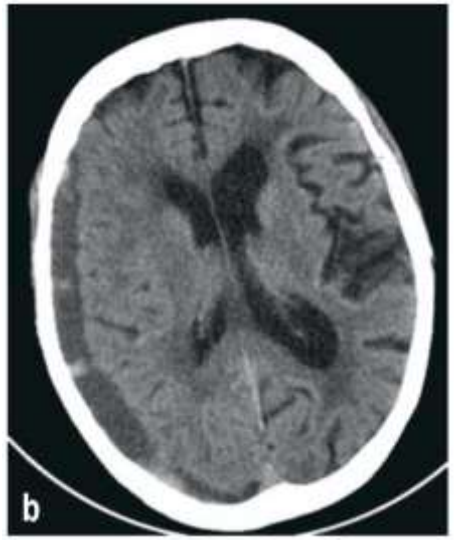
- Höheres Risiko für höhergradige Behinderung und Tod
  - INTERACT 1-Studie: +1ml Hämatomvolumen → 5% erhöhtes Risiko für Abhängigkeit / Tod nach 90 d

- Behandlungsziel: Verhinderung sekundärer Verschlechterung

Eyding J. et al. Neurol Res Pract 2019;1:39; Feigin VL et al. Lancet Neurol 2009; 8(4):355-69; Jolink WM. et al. Neurology. 2015;85(15):1318; Delcourt C. et al. 2012 Neurology.

Was gibt es Neues?

- ANNEX-a-I-Studie – Andexanet alfa zur Antikoagulationsumkehr bei Intrakranieller Blutung
- ENRICH-Studie – Minimal-invasive Hämatomevakuation lobärer ICB
- Last, but not least:

Was hat  mit 

zu tun?

ANNEXa-I

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

Authors: Stuart J. Connolly, M.D., Mukul Sharma, M.D., Alexander T. Cohen, M.D., Andrew M. Demchuk, M.D., Anna Członkowska, M.D., Arne G. Lindgren, M.D., Carlos A. Molina, M.D., +34, for the ANNEXA-I Investigators* Author Info & Affiliations

Published May 15, 2024 | N Engl | Med 2024;390:1745-1755 | DOI: 10.1056/NEJMoa2313040 | VOL. 390 NO. 19

Problem:
Unter vermehrtem Einsatz von Faktor Xa-Hemmern treten häufiger schwere Hirnblutungen auf

Was ist Andexanet alfa (Ondexxya®, Astra Zeneca)?
Einziges spezifisches Antidot zur Antikoagulation bei Rivaroxaban / Apixaban-assoziierten lebensbedrohlichen oder nicht kontrollierbaren Blutungen

Forschungsfrage:
Reduziert Andexanet alfa bei akuter intrakranieller Blutung unter Faktor Xa-Inhibition die Blutungsaktivität wirksamer als die Standardtherapie?

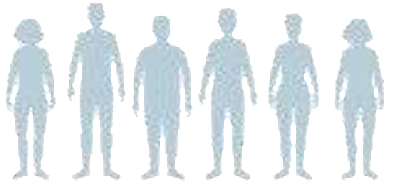
WHY WAS THE TRIAL DONE?

FXa inhibitors are widely used for the prevention of thrombotic events, but they increase the risk of hemorrhage, including ICH. Hematoma volume expansion in ICH is a predictor of poor outcome. The effect of andexanet on ICH volume expansion has not been extensively studied.

HOW WAS THE TRIAL CONDUCTED?

530 patients with acute ICH who had taken FXa inhibitors within the previous 15 hours were assigned to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined as ≤35% expansion of hematoma volume between baseline and 12 hours, a worsening of <7 points in the National Institutes of Health Stroke Scale score at 12 hours, and no rescue therapy between 3 and 12 hours.

PATIENTS



WHO	530 adults
	Mean age, 78.9 years
	Men: 54%; Women: 46%
CLINICAL STATUS	Acute ICH with hematoma volume of 0.5 to 60 ml
	FXa inhibitor use in previous 15 hours

TRIAL DESIGN

- RANDOMIZED
- UNBLINDED TREATMENT; BLINDED DATA ANALYSIS
- PRESPECIFIED INTERIM ANALYSIS
- INTERNATIONAL

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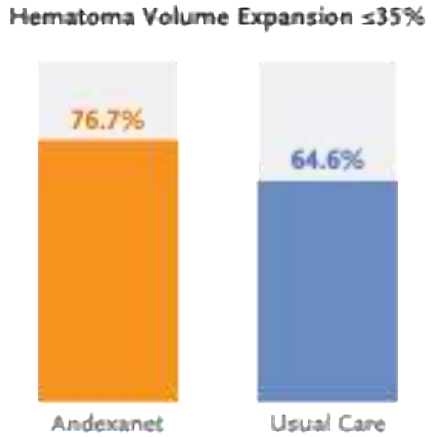
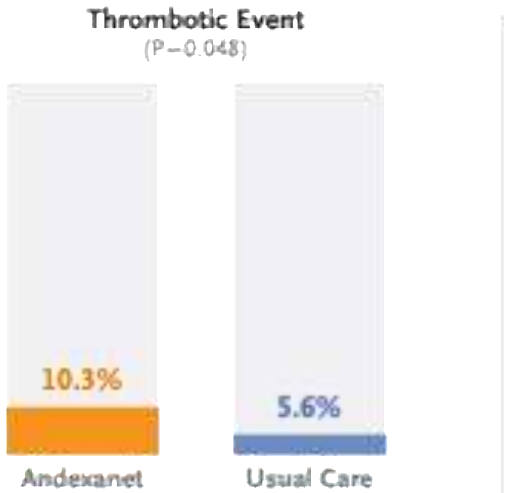
ANNEXa-I

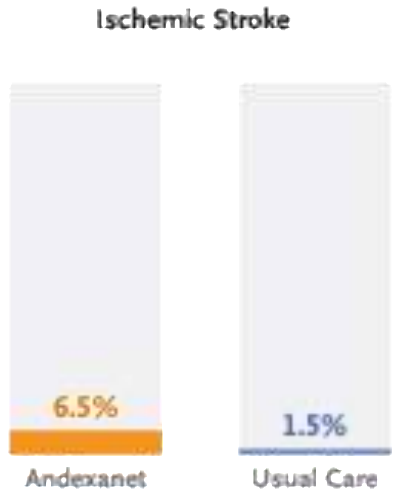
RESULTS

Hemostatic efficacy occurred more often in the andexanet group than in the usual-care group. The difference between treatment groups appeared to be driven by differences in hematoma volume expansion, given that the results for the two other components of the primary end point did not differ appreciably between the groups.

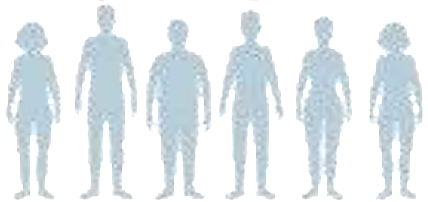
Thrombotic events, including ischemic stroke, were more common in the andexanet group.



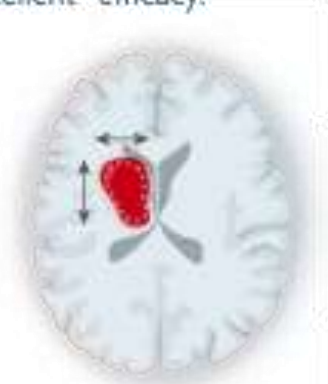




p = 0.048



Most of the patients who met the criteria for hemostatic efficacy had **≤20% expansion of hematoma volume,** defined by the trial as "excellent" efficacy.



≤20%
expansion of hematoma volume

Disability outcomes on the modified Rankin scale were **similar in the two groups.**

Limitations

- Keine langfristigen klinischen Daten
- Wahl der Endpunkte
- Vorzeitiger Studienabbruch

Schlußfolgerung

- Ambivalente Einschätzung
  - Hämatomexpansion reduziert
  - Auf Kosten häufigerer thrombembolischer Ereignisse
  - Einsatz von Andexanet alfa zeigte keine klare Überlegenheit auf relevante klinische Endpunkte wie Behinderung und Mortalität
  - Kosten

The NEW ENGLAND JOURNAL of MEDICINE

Randomized Controlled Trial > N Engl J Med. 2024 Apr 11;390(14):1277-1289.
doi: 10.1056/NEJMoa2308440.

ENRICH

Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage

Gustavo Pradilla [1], Jonathan J Ratcliff [1], Alex J Hall [1], Benjamin R Saville [1], Jason W Allen [1], Giorgio Paulon [1], Anna McGlothlin [1], Roger J Lewis [1], Mark Fitzgerald [1], Angela F Caveney [1], Xiao T Li [1], Mark Bain [1], Joao Gomes [1], Brain Jankowitz [1], Georgios Zenonos [1], Bradley J Molyneaux [1], Jason Davies [1], Adnan Siddiqui [1], Michael R Chicoine [1], Salah G Keyrouz [1], Jonathan A Grossberg [1], Mitesh V Shah [1], Ranjeet Singh [1], Bradley N Bohnstedt [1], Michael Frankel [1], David W Wright [1], Daniel L Barrow [1]; ENRICH trial investigators; ENRICH Trial Investigators

Problem:
Hämatomevakuation spontaner ICB bislang v.a. als lebensrettende Maßnahme etabliert, bisherige Daten unterstützen operative Entlastung nicht. Unklar ist, ob die negativen Studien durch die gewählten Operationstechniken zustande gekommen sind.

Forschungsfrage:
Verbessert minimal-invasive Hämatom-evakuation bei ICB-Patienten das funktionelle Outcome im Vergleich zur Standardtherapie?

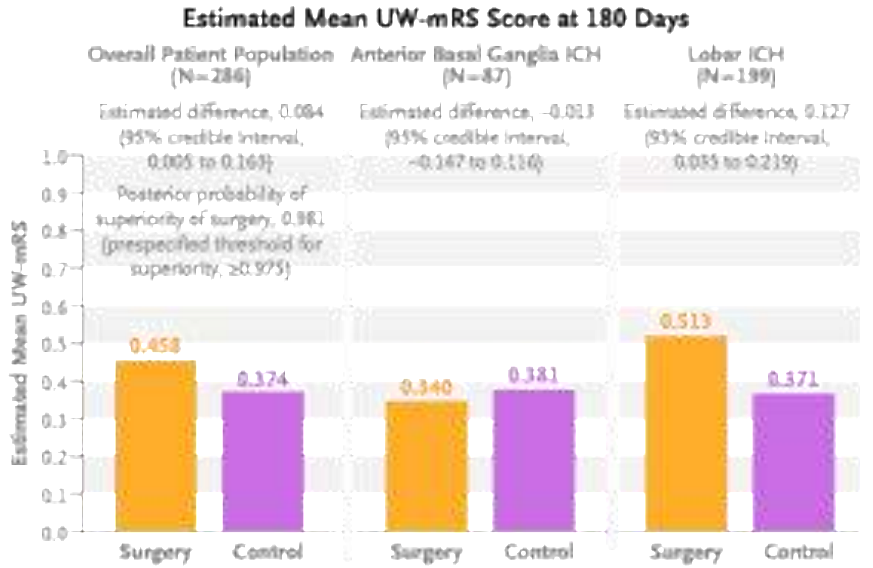
CLINICAL PROBLEM

Current treatment guidelines for a spontaneous intracerebral hemorrhage (ICH) support surgical evacuation of the hematoma by means of conventional craniotomy only as lifesaving treatment, because randomized trials have not shown improvement in functional outcomes except in selected subgroups. Whether early minimally invasive surgical removal of the hematoma might improve functional outcomes is unknown.

CLINICAL TRIAL

Design: A prospective, multicenter, open-label, adaptive, randomized trial assessed early (within 24 hours) minimally invasive surgical removal of the hematoma as compared with guideline-based medical management in patients with an acute supratentorial ICH.

Intervention: 300 adults presenting within 24 hours after a lobar or anterior basal ganglia ICH with a hematoma volume of 30 to 80 ml were randomly assigned to minimally invasive trans-sulcal parafascicular surgery plus medical management or medical management alone. The primary efficacy end point was the mean score for disability on the utility-weighted modified Rankin scale (UW-mRS) at 180 days (range, 0 to 1, with higher scores indicating better outcomes).



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UKM Universitätsklinikum Münster

RESULTS

Efficacy: Among evaluable patients, the mean UW-mRS score was better with surgery than with medical management alone. The benefit of surgery appeared to be attributable to intervention for lobar hemorrhages and not for anterior basal ganglia hemorrhages.

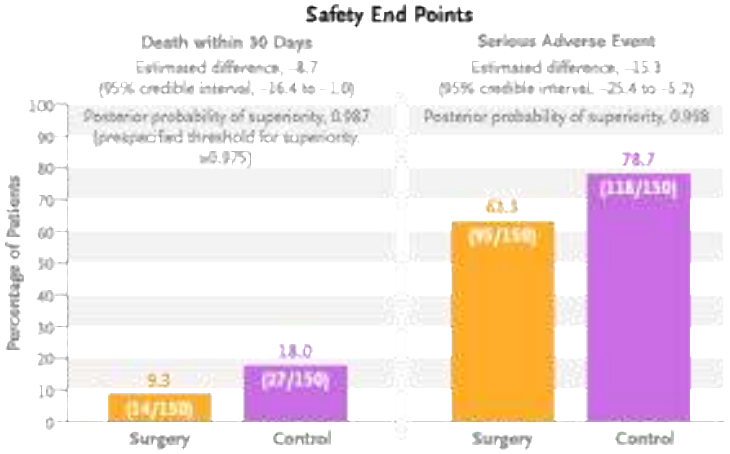
Safety: The percentage of patients who died within 30 days was lower in the surgical group.

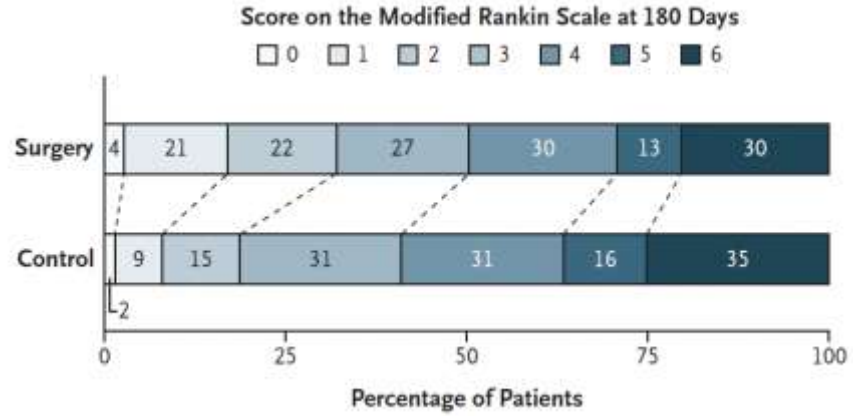
LIMITATIONS AND REMAINING QUESTIONS

- The trial excluded patients with hematoma volumes of <30 or >80 ml and those with substantial thalamic or intraventricular extension.
- Recruitment of patients with anterior basal ganglia hemorrhages was halted for futility after relatively few patients had been enrolled, so inferences of potential benefit in these patients are limited.

CONCLUSIONS

In patients presenting within 24 hours after an acute supratentorial lobar ICH of 30 to 80 ml, minimally invasive surgical evacuation of the hematoma plus guideline-based medical management improved functional outcomes as compared with medical management alone.





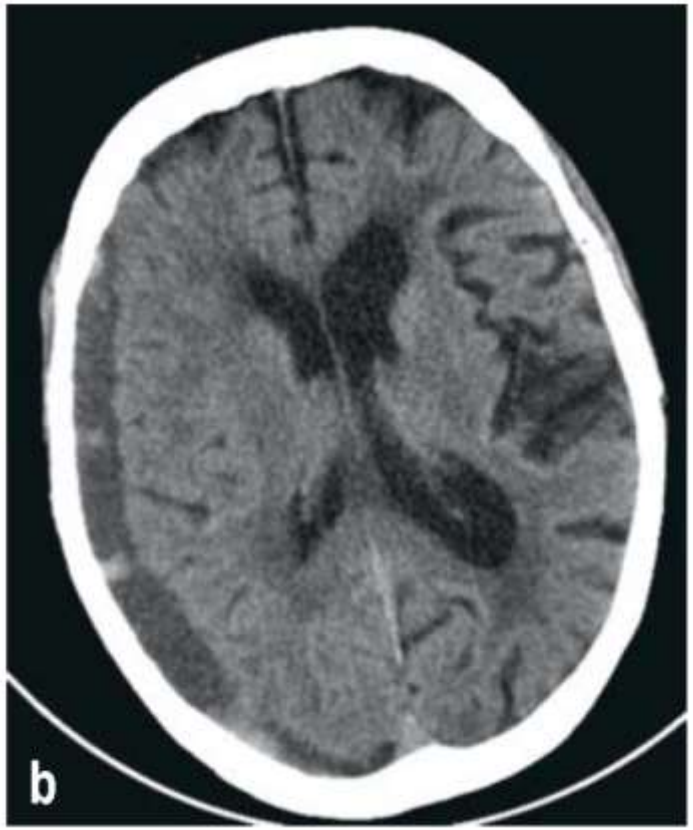
Limitations

- Strenge Einschlusskriterien
  → Generalisierbarkeit unklar
- Keine Langzeitdaten (mRS nach 180 d)
- Einsatz der sog. MIPS-Technik (minimally invasive parafascicular surgery)
  → Keine Aussage über andere chirurgische Techniken

Schlußfolgerung

- MIPS führt zu einem besseren mRS nach 180 d im Vgl. zur Standardtherapie bei supratentorieller lobärer ICB (30 – 80ml)
- Reduktion des Sekundärschadens
- Ähnlicher sicher wie Standardtherapie
- Begrenzter Einfluss auf Mortalität

Uhu und chronisches Subduralhämatom



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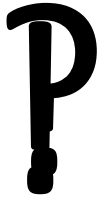

AMM-Embolisation

The NEW ENGLAND JOURNAL of MEDICINE

UKM Universitätsklinikum Münster

EMBOLISE

ORIGINAL ARTICLE

Adjunctive Middle Meningeal Artery Embolization for Subdural Hematoma

J.M. Davies, J. Knopman, M. Mokin, A.E. Hassan, R.E. Harbaugh, A. Khalessi, J. Fiehler, B.A. Gross, R. Grandhi, J. Tarpley, W. Sivakumar, M. Bain, R.W. Crowley, T.W. Link, J.F. Fraser, P. Youssef, M.C. Cress, M.J. Koch, A.R. Paul, W D.H. Sahlein, J. Santar N.V. Patel, C. Roa

MAGIC MT

ORIGINAL ARTICLE

Middle Meningeal Artery Embolization for Nonacute Subdural Hematoma

J. Liu, W. Ni, Q. Zuo, H. Yang, Y. Peng, Z. Lin, Zhenbao Li, J. Wang, Y. Zhen, J. Luo, Y. Lin, J. Chen, X. Hua, H. Lu, M. Zhong, M. Liu, J. Zhang, Y. Wang, J. Wan, Yi Li, T. Li, G. Mao, W. Zhao, L. Gao, C. Li, E Chen, X. Cheng, P. Zhang, Z. Wang, L. Chen, Yongxin Zhang, B. Tian, F. Shen, Y. Lei, Y. Wu, Yanjiang Li, G. Duan, L. Xu, N. Lv, J. Yu, X. X L. Zhang, C. Gao, D. J.M. Ospel, C.B.L.

STEM

ORIGINAL ARTICLE

Embolization of the Middle Meningeal Artery for Chronic Subdural Hematoma

David Fiorella, M.D., Ph.D., Stephen J. Monteith, M.D., Ricardo Hanel, M.D., Ph.D., Benjamin Atchie, D.O., SoHyun Boo, M.D., Ryan A. McTaggart, M.D., Alois Zauner, M.D., Stavropoula Tjoumakaris, M.D., Charlotte Barbier, M.D., Ronald Benitez, M.D., Laurent Spelle, M.D., Laurent Pierot, M.D., Joshua A. Hirsch, M.D., Michael Froehler, M.D., Ph.D., and Adam S. Arthur, M.D., M.P.H., for the STEM Investigators*

DOI: 10.1056/NEJMoa2409845

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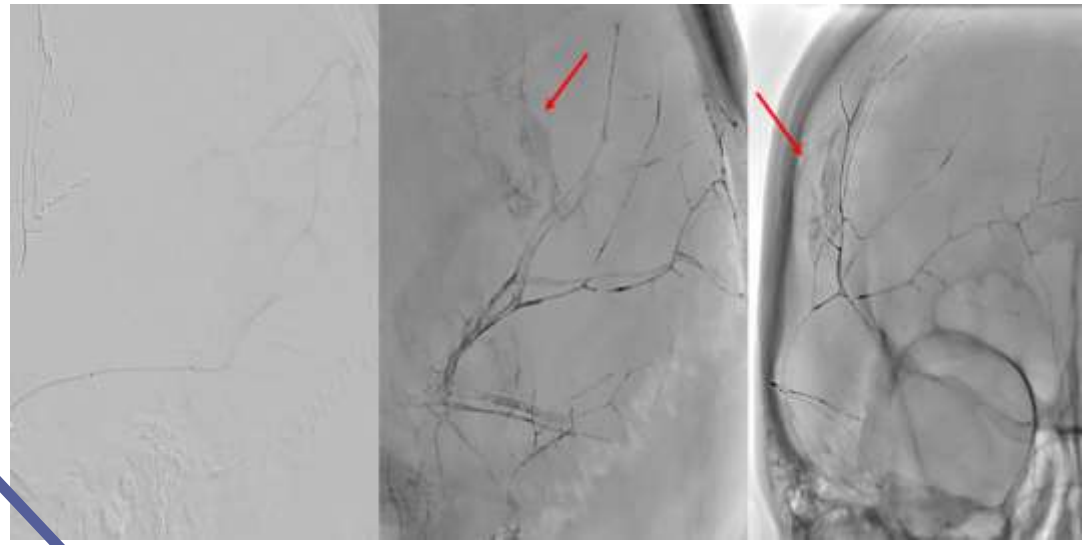
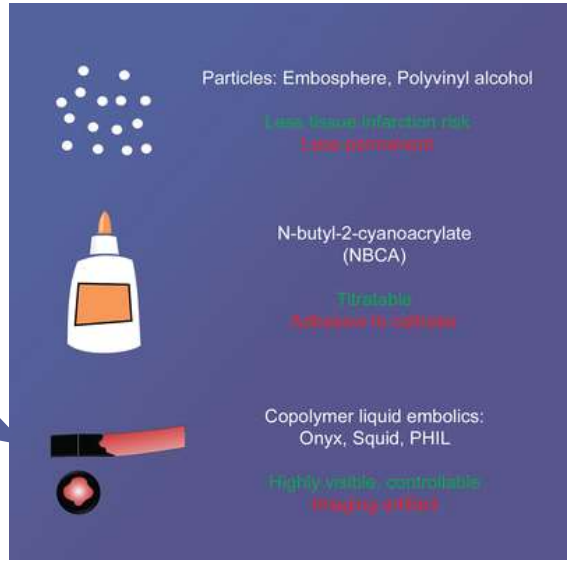


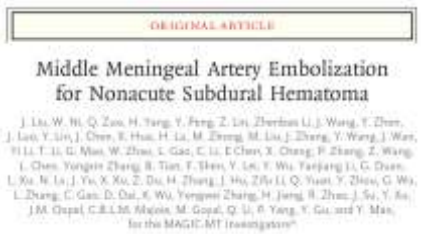
From: Tudor T. et al. Stroke: Vascular and Interventional Neurology. 2023. 4:1



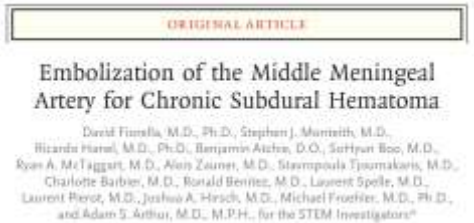
AMM-Embolisation


ORIGINAL ARTICLE

Adjunctive Middle Meningeal Artery Embolization for Subdural Hematoma


ORIGINAL ARTICLE

Middle Meningeal Artery Embolization for Nonacute Subdural Hematoma


ORIGINAL ARTICLE

Embolization of the Middle Meningeal Artery for Chronic Subdural Hematoma

EMBOLISE

Studiendesign:

- Multizentrisch, randomisiert, kontrolliert
- Vergleich von AMM-Embolisation plus chirurgischer Behandlung (Burrhole oder Kraniotomie) vs. chirurgischer Behandlung allein.
- P

Erg

- R

MAGIC MT

Studie

- Mul
- Verg
- Prim

Ergeb

- g

STEM

- Burr
- Red
- Kein
- N

Studiendesign:

- Multizentrisch, international, randomisiert, kontrolliert.
- Vergleich von AMM-Embolisation als Ergänzung zu chirurgischer oder nicht-chirurgischer Standardbehandlung vs. Standardbehandlung allein.
- Primärer Endpunkt: Rezidiv, ausgeprägtes Residuum (>10 mm), Reoperation innerhalb von 180 d
- Primärer Sicherheitsendpunkt: behindernder Schlaganfall, Tod innerhalb von 30 d

Ergebnisse:

- Komplikationen in der Embolisationsgruppe: 16 % (19 von 120 Patienten) vs. 36 % (47 von 129 Patienten) in Kontrollgruppe (OR = 0.36, p = 0.001).
- Behindernder Schlaganfall bzw. Tod innerhalb von 30 d in beiden Gruppen (jew. 3 % in beiden Gruppen)
- mRS nach 180 Tagen ohne signifikanten Unterschied zwischen den Gruppen (p = 0.65)

AMM-Embolisation
Vergleich der Studiendaten

Comparison of trial results for non-surgical and surgical drainage patients with chronic subdural hematoma.

Trials	Non-surgical patients		Surgical patients	
	Efficacy	*P*-value	Efficacy	*P*-value
EMBOLISE	Not reported	Not reported	4.1% vs 11.3%	0.0081
MAGIC MT	1.9% vs 4.7%	Not presented separately	4.7% vs 5.2%	Not presented separately
STEM	19.1% vs 59.2%	0.0001	12.3% vs 25.4%	0.058

Kommentar und Kritik:

- Dropout rate oder „Missing data“ z.T. recht hoch, z.B. EMBOLISE um 10% in Behandlungs- und Kontrollgruppe
  → eingeschränkte Aussagekraft
- Keine signifikanten Effekte in den primär chirurgisch behandelten Gruppen (MAGIC MT und STEM)
- NNT: EMBOLISE n = 14; MAGIC-MT n = 31; STEM n = 5
- Effekte bei nicht primär operierten Patienten whs. die klinisch relevantesten Ergebnisse

Shankar J. et al. Interv Neuroradiol. 2024



Vielen Dank für Ihre Aufmerksamkeit!

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