formation after experimental SAH.

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TRANEXAMIC ACID FOR PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 2991 PATIENTS

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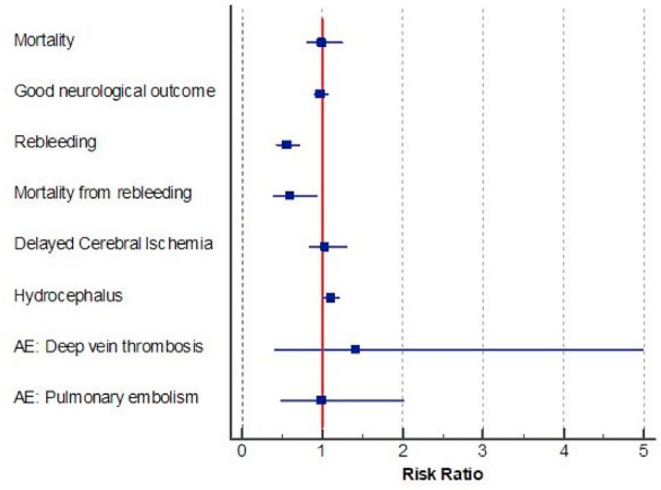
Objective: We aimed to synthesize evidence from published clinical trials on the efficacy and safety of tranexamic acid (TXA) administration in patients with aneurysmal subarachnoid hemorrhage (aSAH).
Methods: We followed the standard methods of the Cochrane Handbook of Systematic Reviews for interventions and the PRISMA statement guidelines 2020 when conducting and reporting this study. A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials was conducted from inception until1 January 2021. We selected observational studies and clinical trials comparing TXA versus no TXA in aSAH patients. Data of all outcomes were pooled as the risk ratio (RR) with the corresponding 95% confidence intervals in the meta-analysis models.
Results: Thirteen studies with a total of 2991 patients were included in the analysis. TXA could significantly cut the risk of rebleeding (RR 0.56, 95% CI 0.44 to 0.72) and mortality from rebleeding (RR 0.60, 95% CI 0.39 to 0.92, P=0.02). However, TXA did not significantly improve the overall mortality, neurological outcome, delayed cerebral ischemia, or hydrocephalus (all$P>0.05$). In terms of safety, no significant adverse events were reported. No statistical heterogeneity or publication bias was found in all outcomes.
Conclusion: In patients with aSAH, TXA significantly reduces the incidence of rebleeding and mortality from rebleeding. However, current evidence does not support any benefits in overall mortality, neurological outcome, delayed cerebral ischemia, or hydrocephalus.



1.2 Arteriovenous Malformations

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COMPLICATIONS IN ENDOVASCULAR NEUROSURGERY

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Introduction: Complications in neurosurgery happen and endovascular neurosurgery is no exception. In comparison with open neurosurgical procedures the complications in endovascular neurosurgery are often irreversible, lead to the development of new focal neurologic deficit and in some cases even fatal outcome. To avoid such complications, we need to fully understand the advantages and disadvantages of endovascular techniques, and select this modality in befitting patients, improving their outcome, while minimizing the risk for them.
Materials and methods: A review of the literature was conducted to identify the most common endovascular complications divided into the following categories: mechanical complications, technical complications, judgement errors and critical events. A comparison analysis was made to our series of 198 consecutive cases for the last two years.
Results: Analyzing the endovascular complications in our series we observed mechanical complications /3.2%/: device deployment, catheter, or closure device failure; Technical complications /4.2%/: unintended embolization, air emboli, retroperitoneal hemorrhage, dissection; Judgement errors /3.5%/: errors in patient or equipment selection; Critical events /5%/: groin hemorrhage, hemorrhagic or thromboembolic complications.
Conclusion: Defining complications in endovascular neurosurgery to measure the overall quality of treatment is difficult, but necessary. Events described as complications during endovascular procedures do not always lead to a negative outcome for the patient. Categorizing complications in endovascular neurosurgery as procedural errors, rather than assessing the overall outcome, morbidity and mortality is a recent approach aiming to assess the procedure related complications leading to negative outcome. Analyzing the pattern of intraoperative adverse events and identifying the reason behind them can lead to their avoidance. Utilizing such an approach with careful preoperative planning, patient selection and choice of endovascular technique can significantly reducethe number of technical, mechanical complications and judgement errors, therefore improving the outcome of our patients.

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PROPRANOLOL AS A POTENTIALLY NOVEL TREATMENT OF ARTERIOVENOUS MALFORMATIONS: FROM BENCH TO BEDSIDE

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Background: Propranolol is a non-selective blocker of the β-adrenergic receptor and has been used for treatment of proliferative infantile hemangiomas. The vasoconstrictive and antiangiogenic effects of propranolol led us to explore its potential application for the treatment of AVMs.
Methods: AVM tissue was cultured after surgical resection in the presence of 100μM propranolol or solvent DMSO. After incubation for 72 hours, tissue was harvested for testing. The expression levels of SDF1α, CXCR4, VEGF and HIF-1 was measured by rt-PCR. Furthermore, data of patients in 2 vascular centres harboring AVM was retrospectively interrogated for a time period of 20 years. The database included information about hemorrhage, AVM size and antihypertensive medication. Descriptive analyses were performed, focusing on the risk of hemorrhage, size of the lesion at presentation and clinical follow-up in patients on β-blocker medication versus those who were not.
Results: Among 483 patients, 73 (15%) were under β-blocker-treatment. 48% AVMs presented with hemorrhage at diagnosis. Patients under β-blocker-treatment had a lower risk of hemorrhage at the time of diagnosis in a univariate analysis (p<0,0001;OR13). Patients under β-blocker-treatment showed a significant higher chance for a lower Spetzler-Martin-grade ≤III (p<0,0001;OR6,5) and a lower risk for the presence of an associated aneurysm (p<0,0001;OR3,6). Multivariate analysis including Spetzler-Martin-Grading, young age ≤50, presence of associated aneurysm and β-blocker-treatment showed reduced risk for hemorrhage under β-blocker-treatment (p<0,01,OR0,2).
The expression of CXCR4 was suppressed by propranolol most likely through the HIF-1-pathways. The gene-expression of vasculogenesis factors was decreased in with propranolol incubated AVMs.
Conclusion: β-Blocker medication seems to be associated with a decreased risk of AVM-related hemorrhage and AVM-size at presentation or during follow-up. Propranolol inhibits SDF1α-induced vasculogenesis by suppressing the expression of CXCR4 most likely through the HIF-1-pathways. Therefore, SDF1α/CXCR4 axis plays an important role in the vasculogenesis and migration of inflammatory cells in AVM lesions.

1.3 Cavernomas

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EFFECTS OF MEDICATION INTAKE ON THE RISK OF HAEMORRHAGE IN PATIENTS WITH SPORADIC CEREBRAL CAVERNOUS MALFORMATIONS

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Background: Recurrent intracerebral haemorrhage (ICH) poses a high risk for patients with cerebral cavernous malformations (CCMs). This study aimed to assess the influence of medication intake on haemorrhage risk in sporadic CCMs.
Methods: From a database of 1409 consecutive CCM patients (2003-2021), subjects with sporadic CCMs and complete magnetic resonance imaging data were included. We evaluated the presence of ICH as mode of presentation, occurrence of ICH during follow-up, and medication intake, including beta blockers, statins, antithrombotic therapy, and thyroid hormones. The impact of medication intake on ICH at presentation was calculated using univariate and multivariate logistic regression with age- and sex- adjustment. The longitudinal cumulative 5-year risk for (re-)haemorrhage was analysed using Kaplan–Meier curves and Cox regression.
Results: A total of 1116 CCM patients were included. Logistic regression analysis showed a significant correlation (OR: 0.520, 95% CI: 0.284-0.951, p = 0.034) between antithrombotic therapy and ICH as mode of presentation. Cox regression analysis revealed no significant correlation between medication intake and occurrence of (re-)haemorrhage (hazard ratios: beta blockers 1.270 [95% CI: 0.703-2.293], statins 0.543 [95% CI: 0.194-1.526], antithrombotic therapy 0.507 [95% CI: 0.182-1.410], and thyroid hormones 0.834 [95% CI: 0.378-1.839]).
Conclusion: In this observational study, antithrombotic treatment was associated with a lower rate of ICH as mode of presentation in a large cohort of sporadic CCM patients. Intake of beta blockers, statins, and thyroid hormones had no effect on haemorrhage as mode of presentation. During the 5-year follow-up period, none of the drugs affected the further risk of (re-)haemorrhage.

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MEDICATION INTAKE AND HEMORRHAGE RISK IN PATIENTS WITH FAMILIAL CEREBRAL CAVERNOUS MALFORMATIONS

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Background and Purpose: To analyze the impact of medication intake on hemorrhage risk in patients with familial cerebral cavernous malformation (FCCM).
Methods: Our institutional database was screened for patients with FCCM admitted between 2003 and 2020. Patients with complete magnetic resonance imaging (MRI) dataset, evidence of multiple CCM, clinical baseline characteristics, and follow-up examination were included. We assessed the influence of medication intake on first or recurrent intracerebral hemorrhage (ICH) using univariate and multivariate logistic regression adjusted for age and sex. The longitudinal cumulative 5-year-risk for (re-)hemorrhage was calculated by applying Kaplan Meier and Cox regression analyses adjusted for age and sex.
Results: 205 patients with FCCMwere included. Univariate Cox regression analysis identified ICH as a predictor for recurrent hemorrhage during the 5-year follow-up (FU). Although not statistically significant, there was a considerably decreased risk of ICH during FU in patients under statin medication (HR: 0.22 [95% CI, 0.03-1.68], P=0.143). No bleeding events were observed in patients under antithrombotic therapy. Kaplan-Meier and log rank test showed a considerable low risk of ICH in patients under antithrombotic (P=0.085), as well as statin (P=0.193) therapy during follow-up. The cumulative 5-year risk of (re) bleeding was 22.82% (95% CI, 17.33%-29.38%) for the entire cohort, 31.41% (95% CI, 23.26%-40.83%) for patients with a history of ICH, 26.54% (95% CI, 11.13%-49.7%) for individuals under beta blocker medication, 6.25% (95% CI, 0.33%-32.29%) for patients under statin medication, and 0% (95% CI, 0%-30.13%) for patients under antithrombotic medication.
Conclusions: ICH was identified as a risk factor for recurrent hemorrhage. Although not statistically significant, statin and antithrombotic medication reveal a trend in preventing bleeding events.

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FEMALE HORMONE THERAPY AND RISK OF INTRACRANIAL HAEMORRHAGE FROM CEREBRAL CAVERNOUS MALFORMATIONS: A MULTICENTRE OBSERVATIONAL COHORT STUDY

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Background: Female hormone therapy (oral contraception in women of reproductive age and hormone replacement therapy in postmenopausal women) are not withheld from patients with cerebral cavernous malformations, although the effects of these drugs on the risk of intracranial haemorrhage are unknown.
Methods: This multicentre observational cohort study included consecutive patients with a cerebral cavernous malformation. We compared the association between use of female hormone therapy and the occurrence of intracranial haemorrhage due to the cerebral cavernous malformation during up to 5 years of prospective follow-up in multivariable Cox proportional hazards regression. We searched OVID MEDLINE and EMBASE from inception to November 2, 2021 to identify comparative studies to calculate the intracranial haemorrhage incidence rate ratio according to female hormone therapy use.
Findings: Of 722 women, aged 10 years or older at time of cerebral cavernous malformation diagnosis, 137 used female hormone therapy. Female hormone therapy use was associated with an increased risk of subsequent intracranial haemorrhage (46/137 [33·6%] versus 91/585 [15·6%], adjusted hazard ratio 1·58, 95% CI 1·10 to 2·27; p=0·012). Use of oral contraceptives in women aged 10-44 years was associated with a higher risk of subsequent intracranial haemorrhage (adjusted hazard ratio 2·05, 95% CI 1·29-3·26; p=0·002). Our systematic literature search showed no studies reporting on the effect of female hormone therapy on the risk of intracranial haemorrhage during follow-up.
Interpretation: Female hormone therapy use is associated with a higher risk of intracranial haemorrhage from cerebral cavernous malformations. These findings raise questions about the safety of female hormone therapy in clinical practice. Further studies evaluating the delivery, dose, and duration of hormone therapy as well as other clinical factors raising risk of thrombosis may be useful to determine which patients may be most susceptible to intracranial haemorrhage.

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HOW CAN WE OPTIMIZE THE LONG-TERM OUTCOME IN CHILDREN WITH INTRACRANIAL CAVERNOUS MALFORMATIONS? A SINGLE-CENTER EXPERIENCE OF 61 CASES

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Background: Pediatric intracranial cavernous malformations (CMs) bear a heterogenous clinical presentation and natural history making decisions for the best management difficult. The objective of this study is to suggest a treatment algorithm based on our institutional experience.
Methods: Patients <18 years of age who were treated at the authors' institution between 1982 and 2019 either surgically or conservatively were retrospectively evaluated. Neurological outcome, seizure outcome and prospective hemorrhage rate was assessed.
Results: In total 61 pediatric patients were treated at the authors' institution, 39 with lobar CMs, 18 with deep CMs including 12 in the brainstem and 6 in basal ganglia. The remaining 4 were located within the cerebellar hemispheres. The median follow-up time was 65 months (1-356 months). In patients with lobar CM, epileptic seizures at diagnosis were more frequently in patients who underwent surgery (72% vs 21%, p=0.003). At last follow-up no difference between