INPLASY

Oedema as a prognostic factor for seizures in meningioma - a systematic review and meta-analysis

INPLASY202370101

doi: 10.37766/inplasy2023.7.0101

Received: 24 July 2023

Published: 24 July 2023

Corresponding author:
Matthew Tanti

m.tanti@nhs.net

Author Affiliation:
University of Leeds.

Tanti, M[1]; Nevitt, S[2]; Yeo, M[3]; Bolton, S[4]; Chumas, P[5]; Mathew, R[6]; Maguire, M[7].

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202370101

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2023 and was last updated on 24 July 2023.

INTRODUCTION

Review question / Objective Meningiomas are often associated with seizures and oedema and there is interest in predicting seizure outcomes for patients with meningioma. Oedema is often cited as a prognostic factor for seizures but there is scope for an updated systematic review and meta analysis to address this association at various stages of the treatment journey.

Rationale Englot et al published a systematic review and meta-analysis in 2016 looking for prognostic factors for seizures; only eight of 33 studies measured oedema as considered it a prognostic factor for preoperative seizures. Their pooled analysis revealed that oedema was associated with an increased odds of preoperative seizures (odds ratio 7.48; 95% CI 6.13 to 9.47; 8 studies; 1095 participants). Only three studies (n=244) considered oedema for postoperative seizures but there was insufficient data to perform a meta-analysis.

Examining risk predictors for seizures in meningioma and the effect of pre and post-treatment peri-tumoral oedema as a prognostic factor by updated review may enable the development of more robust prognostic modelling across the treatment pathway. This may facilitate early and more successful treatment of seizures and oedema which could positively influence treatment outcomes.

Condition being studied Meningiomas are common neoplasms that arise from the meningeal coverings of the central nervous system. Oedema is commonly seen at diagnosis, with reported proportions varying from 40% to 80%. Seizures can occur at any time point with meningioma, even many years after resection. They are a presenting feature for 30% and recur postoperatively in 30%. Seizure risk in meningioma is modified by tumour characteristics such as size, location and presence of brain invasion or oedema, but also impaired performance status.

METHODS

Search strategy A comprehensive search for trials and observational studies was performed with no date limitation up to the current date (week 3, January 2023). One author will perform the search with the following search engines:
• Ovid* (Wolters Kluwer)
• Scopus (Elsevier)
• Web of Science (Clarivate)
• Pubmed (U.S. National Library of Medicine)
• Medline (via pubmed)
• ClinicalTrials.gov (U.S. National Library of Medicine)
• Google scholar
OVID searches include the following databases*:AMED (Allied and Complementary Medicine) 1985 to January 2023, BIOSIS Previews Archive 1926 to 1968, CAB Abstracts 1910 to 2023 Week 03, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 18, 2023, EBM Reviews - ACP Journal Club 1991 to December 2022, EBM Reviews - Cochrane Clinical Answers January 2023, EBM Reviews - Cochrane Central Register of Controlled Trials December 2022, Embase Classic+Embase 1947 to 2023 January 24, Global Health 1910 to 2023 Week 03, Maternity & Infant Care Database (MIDIRS) 1971 to December 20, 2022, APA PsycInfo 1806 to January Week 3 2023, Leeds University Library's Journals@Ovid (full text), Leeds University Library's Books@Ovid (full text), HMIC Health Management Information Consortium 1979 to November 2022 Search strategies will include the terms "meningioma", "oedema", "seizures/epilepsy" with boolean operators and truncation where allowed or multiple searches with additional acronyms, spellings and expansions to optimise search terms for each database.

Participant or population Adults or children with a diagnosis of meningioma and data on their seizure and oedema status will be included. Extracranial meningioma will be excluded for example spinal meningioma or optic nerve meningioma without intracranial extension. Patients with a non-meningioma diagnosis will be excluded (e.g. glioma, lymphoma, meningioangiomatosis, Rosai Dorfman disease). Non-human participants will be excluded. Participants without measurement of seizure or oedema status will be excluded.

Intervention NA - prognostic factor research.

Comparator NA - prognostic factor research.

Study designs to be included To be considered for inclusion, an original unique study must include patients with data on oedema and seizure status. It is anticipated that most studies will be retrospective case-control or cohort studies but all study designs will be considered including prospective cohort, cross sectional and randomised or non-randomised trials. Studies of case reports and small case series with less than 10 meningioma patients will be excluded. Reports will be included irrespective of language or peer review status.

Eligibility criteria Titles and abstracts will be screened by one author for inclusion. If the abstract or title is clear that the study meets exclusion criteria, and does not meet inclusion criteria, it will be excluded. If it is unclear the report will be reviewed. If a report is unavailable, and it might meet inclusion criteria, the University library will be contacted to assist in sourcing reports, and if unsuccessful the authors will be contacted. A well written abstract would be considered if the full report was not available, and it contained sufficient information of population, oedema and seizure status. Studies that consider the relationship between oedema and epilepsy in intracranial meningioma will be reviewed by two authors to determine whether it will be used for meta-analysis or narrative review. Reports will be checked to ensure they are not reporting the same study by one author. For inclusion to the meta-analysis, studies must present data comparing patients with and without seizures and oedema. If dichotomous oedema or seizure data are measured then a contingency table or unadjusted effect size with odds ratio (OR) or risk ratio (RR), and 95% confidence interval (CI) should be presented or extractable. Ordinal data will be extracted as presented. If continuous oedema data are presented then the standardised mean difference should be calculable and will require the number of participants in each group, group means and standard deviations (SD) or alternatively the standardised mean difference (SMD) and 95% CI could be reported. Plot digitizer will be used to extract data from graphs if needed. If insufficient data is included in original studies, authors will be contacted for more information. It is unlikely for seizure outcomes to be measured on continuous scales but this will be collected and considered if present.

Information sources All sources of unique studies will be considered and will include, and is not limited to, peer reviewed journal articles, poster abstracts, conference proceedings and book chapters. If a report makes reference to potentially relevant study, that study will be reviewed and considered for inclusion. Furthermore review

articles and commentaries will be reviewed in case they contain relevant unique studies not otherwise identified.

Main outcome(s) Oedema will be the prognostic factor for this study. It can be identified by magnetic resonance imaging (MRI) or computed topography (CT) scanning. It can be measured at any timepoint and will be categorised as pre-treatment, early post treatment (within a week), late post treatment (more than a week), or unknown. Oedema is usually measured as follows:
• binary variable (e.g. present or absent, or, present or minimal)
• ordinal (e.g. absent, mild, moderate, severe)
• continuous (e.g. oedema volume)
• oedema index (e.g. oedema volume divided by tumour volume)
Epilepsy will be health outcome for this study. Epilepsy is usually defined as the tendency for unprovoked seizures although epilepsy and seizures are terms that are often used interchangeably in the literature. Seizures can be provoked by surgery hence the distinction between early and late post-treatment seizures. Both seizures and epilepsy will be considered in this review. Seizures/epilepsy will likely be measured as a binary variable (present or absent) but will also be considered if expressed as an ordinal or continuous variable if presented both in patients with and without oedema. Like oedema it can be measured at any timepoint and will be categorised as pre-treatment, early post-treatment (within a week), late post-treatment (more than a week), or unknown.
A separate analysis will be considered for each time-point relative to treatment (surgery and radiotherapy):
• pre-treatment oedema and pre-treatment seizure
• pre-treatment oedema and early (within one week) post-treatment seizure
• pre-treatment oedema and late (later than one week) post-treatment seizure
• post-treatment oedema (early or late) and subsequent post-treatment (early or late) seizure
• pre-treatment seizure and post-treatment (early or late) oedema.

Additional outcome(s) As a secondary outcome, the results from the primary meta-analysis will be sub-grouped according to other covariates of interest which if present in sufficient quantity will include:
• oedema definition or measurement method
• seizure definition
• any covariate used to subgroup patients with seizures or oedema when comparing patients with and without seizures by oedema

In addition, other prognostic factors used in univariate and multivariate regression analyses to predict seizures in meningioma subjects will be collected irrespective of whether a significant association exists and irrespective of whether oedema was included in the regression. This will be performed at the time points pre-treatment, early post-treatment (within a week), late post-treatment (more than a week), or unknown and will be reported in a narrative review as mentioned in the secondary objectives.

Quality assessment / Risk of bias analysis Risk of bias will be assessed by one author for all studies, and will depend on study type, using the following tools:
• Randomised control trials (RoB 2)
• Non-randomised trials (ROBINS-I)
• Exposure outcome observational studies (ROBINS-E)
These tools assess bias over a range of domains before an overall bias score will be surmised. This will be presented with the Robvis visualisation tool.

Strategy of data synthesis The meta-analysis will be performed using the R-project programming tool using the “meta”, “metafor” and “dmetar” packages as required with the “Doing Meta-Analysis with R” guide. Mantel-Haenszel method without continuity correction will be used to meta-analyse binary outcomes. Inverse-variance method will be used to meta-analyse continuous outcomes. A random-effects model will be used as it is anticipated that the studies will be relatively heterogenous.
Studies included in the meta-analysis will be assessed for between study heterogeneity primarily by using Higgins & Thompson’s I2 statistic and the heterogeneity variance τ2.[58] Interpretation of I2 will be as follows; 25%: low heterogeneity, 50%: moderate heterogeneity, 75%: substantial heterogeneity. Different methods can estimate τ2. For continuous outcome data, the restricted maximum likelihood estimator will be used and for binary effect sizes the Paule-Mandel estimator. Different τ2 will be used such as DerSimonian and Laird to investigate the influence of the method used to estimate τ2 on the meta-analysis results.
The standard deviation of true effect sizes τ, Cochran’s Q and the H2 statistic are also standard outputs in the R program when estimating heterogeneity. Prediction intervals will also be used to see if effect size direction is likely to be similar for future studies.

Subgroup analysis As part of an assessment of heterogeneity each study will be assessed for

confounding variables and if possible a subgroup meta-analysis and meta regression will be performed. Risk of bias will be used as a grouping variable. It is anticipated that the studies in this report will be heterogenous on account of the heterogeneity within meningioma behaviour, oedema definitions, oedema measurement techniques, thresholds for identifying seizures, differing follow-up, and variations in healthcare amongst different neurosurgical centres.

Sensitivity analysis Outlying studies can be detected and removed by the R program if the confidence interval does not overlap with the pooled confidence interval. Further influence diagnostics will be performed to determine and plot the influence and heterogeneity of each study therefore assessing how robust the pooled effect size is.

Language restriction None.

Country(ies) involved United Kingdom.

Keywords meningioma; seizures; epilepsy; oedema; edema; prognostic factors; systematic review; meta-analysis.

Dissemination plans Publication in peer reviewed paper and write up in MD thesis for storage in University repository.

Contributions of each author

Author 1 - Matthew Tanti - Lead author. Drafted protocol and manuscript. Data extraction and analysis.
Email: m.tanti@nhs.net
Author 2 - Sarah Nevitt - Statistical advice. Review and design of protocol.
Email: sjn16@liverpool.ac.uk
Author 3 - Molly Yeo - Data validation.
Email: molly.yeo@nhs.net
Author 4 - William Bolton - Data validation.
Email: w.s.bolton@leeds.ac.uk
Author 5 - Paul Chumas - Review of protocol.
Email: p.chumas@nhs.net
Author 6 - Ryan Mathew - Joint senior author. Review of protocol.
Email: r.k.mathew@leeds.ac.uk
Author 7 - Melissa Maguire - Joint senior author. Review of protocol. Review of statistical methods.
Email: melissamaguire@nhs.net