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Review article

The role of prophylactic antiepileptic drugs for seizure prophylaxis in meningioma surgery: A systematic review

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ABSTRACT

Meningiomas are the commonest type of primary brain tumours. Whilst most patients are seizure-free prior to surgery, antiepileptic drugs are frequently administered to reduce the risk of developing post-operative seizures. However, evidence to support their efficacy in providing this outcome is sparse. To this end, we performed a systematic review to assess the impact of prophylactic antiepileptic drugs on post-operative epilepsy rates in seizure-naïve patients undergoing craniotomy for resection of meningiomas. The literature search was performed using PubMed for studies published between January 1990 and November 2016. The total number of patients in each study was extracted and divided into cohorts according to administration of prophylactic antiepileptic drugs. Clinical characteristics, study type and post-operative epilepsy rates were recorded. A total of 11 studies involving 1143 patients met the selection criteria. There was no statistically significant difference in the number of patients who developed post-operative epilepsy in the cohort that received prophylactic antiepileptic drugs (20 of 766; 2.6%) and the cohort that did not (10 of 377; 2.7%) (Chi-square test; $P = 0.96$). A detailed meta-analysis could not be performed due to the insufficiency in data reported. Based on the results of this systematic review, the routine use of antiepileptic drugs for seizure prophylaxis in seizure-naïve patients undergoing meningioma resection could not be substantiated. However, limitations of a systematic review should be considered on interpretation. High quality prospective randomised controlled trials are required to definitively answer this important clinical question.

1. Introduction

Meningiomas are the most common primary brain tumours, accounting for approximately a third of all intracranial neoplasms and with an estimated incidence rate of 5 per 1,00,000 person-years in the UK [1,2]. The World Health Organisation (WHO) classifies these tumours into three groups: benign meningioma (grade I), atypical meningioma (grade II) and anaplastic meningioma (grade III) [3]. Approximately 90% of meningiomas discovered are benign and asymptomatic; the remainder go unnoticed until they clinically manifest in the form of headaches, seizures or other neurological problems [4]. This indicates that the majority of patients are free of seizures at the time of diagnosis and remain so up until the time of surgery [5]. Despite this, antiepileptic drugs (AEDs) are frequently prescribed peri-operatively in an attempt to reduce the risk of seizures post-craniotomy albeit being rather evidently unfounded. Furthermore, a recent Cochrane review on the routine administration of AEDs post-operatively for brain tumours, including meningiomas, concluded there was little evidence to recommend routine use [6]. In addition to the risk of acute adverse drug reactions, recent studies have suggested that AEDs may also limit neurological recovery due to their effects on cognitive function [7]. Nonetheless, the consequences of post-operative seizures include major morbidity from cerebral oedema, reduced quality of life, [8] cognitive issues and loss of driving licence, but the rate at which new seizures develop in patients undergoing meningioma surgery has been inconsistently and variably reported over the last four decades and ranges from 0.5 to 22% [9–11]. When all of the aforementioned factors are taken into consideration, they present a challenge to the clinician whose responsibility is to measure the potential benefits of AED prophylaxis against the adverse effects. Several reviews have previously addressed this issue, however, these include older studies that pre-date more modern

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micro-neurosurgical practice [12–14]. The role of prophylactic AEDs in meningioma surgery has also been the topic of regular editorials and opinion pieces that highlight the unresolved clinical dilemma [15,16]. The aim of this study was to perform a systematic literature review to determine the association between prophylactic AEDs and the risk of post-operative epilepsy in seizure-naïve patients undergoing meningioma resection.

2. Methods

2.1. Study selection

A filtered literature search was performed using the US National Library of Medicine PubMed database. Filters applied were Language, which had been set as English, and a date range from 01/01/1990 to 30/11/2016. The search term utilised was (*"Meningioma"[Mesh] AND ("Postoperative Period"[Mesh] OR "Postoperative Complications"[Mesh] OR "Treatment Outcome"[Mesh] OR "Epilepsy"[Mesh] OR "Seizures"[Mesh] OR "Risk Assessment"[Mesh])) OR ("Meningioma" AND ("Treatment Outcome" OR "Epilepsy" OR "Seizures")*). This term incorporated Medical Subject Headings (MeSH) in conjunction with their counterpart keywords to ensure that relevant MeSH-unindexed records were included. The titles of all results were screened. Abstracts were reviewed with titles that mentioned intracranial meningiomas or brain tumours in combination with seizure, epilepsy, antiepileptic drugs, surgical outcome or anything of similar construct. Full-text articles were inspected if from the abstracts the number of seizure-naïve meningioma patients could be discerned to be more than 15 and if reported outcomes could have possibly incorporated seizures or epilepsy. For inclusion, full-text articles were subjected to the following selection criteria:

1. The number of seizure-naïve meningioma patients $\geq$15.
2. The duration of follow-up $\geq$1 month.
3. The neurosurgical approach was craniotomy based.
4. Post-operative seizure data was available for seizure-naïve patients.
5. A clear statement on whether prophylactic AEDs had been used or not was present.

Data for patients <16 years of age was omitted. A reference list search on all relevant papers was also undertaken to identify any further relevant studies. The search was carried out by A.I.I, S.M and T-E.K-O. Articles identified were only included upon mutual agreement. Corresponding authors of articles that created a dispute amongst the authors due to their ambiguity were contacted via e-mail by A.I.I to ascertain additional data that could help resolve such disputes. Articles for whom authors did not provide a response were dismissed. Records supplemented by further communications were reviewed again and included upon mutual agreement. M.D.J verified and approved the final set of papers.

2.2. Data extraction

Patient characteristics, study type (retrospective, prospective, randomised controlled trial), AED use and post-operative outcomes were recorded. The outcomes of interest were extent of resection (as defined by each study), occurrence of post-operative seizures, and AED-associated adverse reactions. For each study, patients were divided into two cohorts: patients that received prophylactic AEDs and those who did not. Seizures occurring within one week of surgery were classed as "early", and "late" if they occurred after one week. Data for all seizure-naïve patients were recorded when available including: age, gender, features of meningioma, and AED used.

2.3. Statistical analysis

Due to limitations in the available data and variation in outcome reporting it was not possible to perform a detailed meta-analysis. Descriptive statistics were used. For comparisons between the cohorts receiving AED prophylaxis and those not, Chi-square test was employed. Differences were considered to be statistically significant at $P < 0.05$. Statistical analyses were conducted using IBM SPSS Version 24.0 (SPSS Inc.).

3. Results

3.1. Literature search

Fig. 1 describes the study selection process. The filtered PubMed search identified 2321 records. The number of abstracts screened was 254, and the full-text articles of 114 of those abstracts were reviewed. The initial number of articles excluded and included was 99 and 8 respectively. The corresponding authors of 7 articles were contacted and only 3 of those articles were included in the final analysis. No additional articles were identified on review of references. The final number of articles included was 11, with an overall population of 1473 patients.

3.2. Study characteristics

The characteristics of the 11 studies are summarised in Table 1. Eight papers investigated meningioma resection in patients that received prophylactic AEDs: 3 prospective [10,17,18] and 5 retrospective [19–23]. One prospective study investigated meningioma resection in patients that were not administered AEDs [24]. The remaining 2 papers were retrospective and had mixed cohorts [11,25]. The occurrence of post-operative seizures was the primary investigated outcome in only 4 studies [10,11,17,25]. One study was multi-centred [24] whilst the rest were single-institution studies. There were no prospective randomised controlled trials.

3.3. Patient characteristics

The total number of patients was 1473, with a mean age of 56.8 years (range 18–95 years). The follow-up period ranged from 1 to 222 months. For the purpose of this systematic review, only seizure-naïve patients were included ($n = 1143$). A total of 766 patients who received prophylaxis constituted the AED cohort. The remaining 377 patients formed the No-AED cohort. The differences in proportions of non-skull base (% of valid cases = 29.5; 100% vs 46.9%; $P < 0.05$) and WHO grade I (% of valid cases = 64.8; 85.7% vs 75.2%; $P < 0.05$) meningiomas amongst the two cohorts were statistically significant. The remaining characteristics, detailed in Table 2, were either balanced or incomparable.

3.4. Antiepileptic drug characteristics

The AEDs that were utilised in seizure-naïve patients are detailed in Table 3. Selected doses for AEDs were not reported. Duration of AED administration was only described in 1 study, where patients received a one week treatment course post-operatively [11]. No studies reported whether pre-operative AEDs were switched post-operatively in peri-operative prophylaxis. The discontinuation or withdrawal process was not outlined in any of the studies.