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Effectiveness of antiepileptic prophylaxis used with supratentorial craniotomies: a meta-analysis

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Thirty publications on the effectiveness of prophylactic antiepileptic drugs (AEDs) with supratentorial craniotomies were reviewed (1980–1995). After a first selection, six controlled studies remained (11 publications). These six were evaluated according to previously defined methodological criteria. The criteria were divided into three main categories: (1) internal validity, (2) proper and relevant outcome-measures and (3) analysis. In this way a maximum of 145 points could be obtained for each study. Three studies were considered to be of satisfactory methodological quality (≥55% of 145 points) and the odds ratios were calculated as a measure of association between treatment and occurrence of convulsions. The odds ratios of these three studies were statistically pooled using the Mantel-Haenszel Estimator. From this test it appeared that prophylactically used AEDs showed a tendency to prevent postoperative convulsions, but this effect was certainly not statistically significant ($P = 0.1$ one-tailed). Points of attention concerning possible future investigations are stressed.

Key words: epilepsy prophylaxis; meta-analysis; postoperative seizure; seizure prophylaxis; supratentorial craniotomy.

INTRODUCTION

For years there has been uncertainty and a debate, especially between neurosurgeons and neurologists, about the usefulness of antiepileptic drugs (AEDs) prophylactically, to prevent postoperative convulsions after supratentorial intracranial surgery. Many neurosurgeons prefer the use of prophylactic AEDs because surgical results can be severely compromised by postoperative epileptic seizures[1]. ***In the early postoperative period cerebral oedema, due to surgical manipulation, may contribute to increased intracranial pressure. A seizure causes cerebral hypoxia and acidosis and may lead to a further elevation of the intracranial pressure, hereby altering the level of consciousness of the patient and making postoperative clinical evaluation difficult. Intra-cerebral haemorrhages can be masked and may lead to catastrophic events. Additionally cerebral hypoxia in the course of a disease process constitutes a severe hazard to the patient***[2,3]. Another argument to prevent postoperative epileptic seizures (PES) is that they may possibly lead to secondary epileptogenic foci (kindling), however ***this is shown in animal studies and scientific research has stil not shown that it is applicable to the human brain***[4,5]. On the other hand, many neurologists argue that a single epileptic convulsion, even if it is postoperative, does not justify the diagnosis of epilepsy, or long-term prophylactic treatment. Furthermore, the adverse effects of the AEDs (rash, gingivahyperplasia, coarsening of the skin) could well surpass possible advantages of treatment.

Until recently, clinical review articles concerning the prophylactic use of AEDs often relied on the authors' subjective selection and interpretation as well as the use of unpublished information related to the clinical topic. In most publications no explicit criteria were used, leaving any derived recommendations open to bias and error[6]. Therefore at this moment an increasing amount of review articles and meta-analyses are characterized by more explicit and quantitative methods of synthesizing data. Meta-analyses of ran-

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domized controlled trials have been helpful not only to answer particular research questions, but also in the formulation of practical guidelines, for planning further clinical trials, and as a means of providing data required for the performance of decision analyses and cost-effectiveness analyses[6].

We analysed and evaluated the methodological quality of the studies as it was presented in the publication(s) on the effectiveness of prophylactic AEDs. Previously defined criteria were used in the assessment, a process which is commonly referred to as 'criteria-based meta-analysis'[6,7]. Selected studies of sufficient methodological quality were statistically pooled. By means of this procedure it is attempted to obtain an overall conclusion concerning the effectiveness of prophylactic AEDs with intracranial supratentorial surgery.

METHODS AND MATERIALS

Literature-search strategy

First, a MEDLINE computersearch[8] was performed using the keywords: preoperative, anticonvulsants, prophylactic, phenytoin, phenobarbital, carbamazepine, postoperative, epilepsy, craniotomy. With the help of a CD-ROMsystem all publications between January 1980 and November 1995 that contained one, or a combination of more keywords, were located. Second, the same strategy was applied to the Excerpta Medica (1984–1995). Finally, the reference-listings of the publications were scanned for further eligible publications from the same period.

Literature selection

Publications were eligible to be included in the criteria-based meta-analysis if the publication reported a clinical trial and index, and control groups were used (reviews and editorials were ruled out). The patient-population in the trial had to undergo a supratentorial craniotomy for either therapeutic or diagnostic reasons. Head trauma in itself is a well recognized cause of epilepsy and although the underlying mechanisms that causing epilepsy appear to be similar to those of PES, including patients with head trauma could possibly bias trial outcome. For much the same reason, publications which included patients with preoperative epileptic seizures were not selected (if there was a part of the patient-population in the trial that had had preoperative convulsions and/or intracranial surgery because of a neurotrauma, but which was easily separable from the part that did not, then that study was considered to be eligible for further analysis in the criteria-based meta-analysis).

AEDs used in the trial consisted of one, or a combination of the following: phenytoin, carbamazepine, barbiturates. The time of administration of the AED-prophylaxis was within one week prior to surgery until one day after surgery. The language of the publication was either English, German, French, or Dutch.

Scoring of quality

The weight of each criterion is expressed by a maximum number of points and depends on the issue of the meta-analysis. The total score for all 22 criteria consisted of a maximum of 145 points (Table 1). For each criterion a certain number of points could be obtained, depending on the extent to which its requirements were met. The total score of the study was expressed as a percentage of the maximum of 145 points. The percentage was used as an indication of the methodological quality of the trial presented in a publication.

The number and the way in which points were assigned to the different criteria reflects the ideas of the authors of this review-article. Therefore, the data are presented in such a way that the reader is able to verify the scores and reset them to his/her own opinion. Table 1 lists all the criteria that were used in the meta-analysis with their maximum scores. Particular criteria which are divided in subcriteria are explained below the table. Arbitrarily a score of 55% was decided to be the cutoff point for good methodological quality.

In our overall judgement of the effectiveness of AEDs in the prevention of epileptic seizures after supratentorial craniotomies, we only used results from trials of studies that obtained at least 80 points (55% of 145).

Statistical analysis

As the general effect-parameter for all studies the odds ratio (OR) was used. The odds ratio represents the association between treatment and the occurrence of postoperative seizures. If the odds ratio equals 1, then the effect of treatment

Table 1: Criteria, with different weight-factors, used for scoring the methodological quality of a study

Criteria	Weighting
Internal validity	
Comparability of prognosis	
Homogeneity (1)	10
Prestratification (2)	3
Randomization	10
Randomization procedure described	3
Comparability of relevant baseline characteristics shown (3)	5
Number of patients per group (4)	3/5/7
Percentages of patients lost to follow-up (5)	4/7
Intervention and external variables	
Plasma-levels of anti-epileptics adequate (6)	15
Dose anti-epileptics adequate (7)	3
Compliance (8)	4
Intervention procedures adequately described (9)	10
Effect measurement	
Patients blinded (10)	10
Evaluator blinded	5
Check-up blinding	2
Proper and relevant outcome-measures	
Remark on side effects (11)	7
Remark on difference of seizure-frequency between groups	10
Remark on type of postoperative convulsions	5
Follow-up in months after treatment (12)	3/7/9
Analysis	
Data prêsentation (13)	5
Intention-to-treat analysis	5
Description of methods of analysis	5
Influence of confounding variables minimized (multi-variate analysis)	5

If a publication fulfilled all criteria completely a total score of 145 points could be reached.
(1) Pathology of the patient is in this meta-analysis considered as the most important prognostic factor, if the groups were comparable on this item 5 points were given. If other important prognostic variables were mentioned(operation-time, age of patient, manipulation of the brain, side of laesion, systemic diseases associated with high risk of seizures) extra points were given to a max. of 5. (2) If prestratification is mentioned or if the item 'homogeneity' scores higher than 5, three points are given. If the groups contain less than 50 patients each and there is no prestratification, 3 points are subtracted. (3) 5 points if characteristics are arranged in the form of a table. 3 points if characteristic were only mentioned in the text. (4) ≤50 patients per group: 3 points, 51–100 patients: 5 points, >100 patients: 7 points. (5) ≤10% loss to follow-up: 7 points, 11%–20%: 4 points, >20%: 0 points. (6) If 100% of the patients in the intervention-group have therapeutic plasma-levels 15 points are given, e.g. 66% of the patients have therapeutic levels, 66% of 15 points is 10 (10 points were given). (7) 3 points if minimal dose agrees with Sonnen's (9) recommendation. (8) 2 points if compliance was mentioned in patient number or in proportion. An extra of 2 points is given if the reason of non-compliance was mentioned. (9) For each of the following items 1 point can be scored; generic name of anti-epileptic medication, duration of intervention, method of administration of anti-epileptics, dose and number of administration per day. The following items are scored in a different way; plasma-levels controlled 2 points, if not mentioned −2 points; frequency/interval of plasma-level assessment, 2 points; therapeutic range mentioned 2 points, if not −2. On this methodological item a maximum score of 10 points can be reached. (10) To a maximum of 3 points was given depending on the description of similarity between the placebo and the intervention-medication. (11) The max. of 7 points are divided in; 3 points for summing-up the side-effects, and 4 points for the number of patients having these side-effects. (12) ≤3 months: 3 points, >3 months: 7 points, ≥12 months: 9 points. (13) Between 3 and 5 points are given dependent on the comprehensiveness of data presentation.

vs. the effect of no treatment shows no difference at all in respect to prevention of postoperative seizures. If the effect of treatment is superior to no treatment, the odds ratio will be below one (e.g. OR = 0.5 indicates a reduction of about 50%). On the other hand, an odds ratio above 1 indicates that the placebo-treatment is more effective than prophylactic AED-treatment.

To pool the odds ratios of the different trials the Mantel–Haenszel Estimator[10] was used and 95%-confidence-intervals and the *P*-value were determined (see Fig. 1).

RESULTS

A total of 30 publications was found using the CD-ROM Medline and Excerpta Medica. Three Japanese publications[1,11,12] were excluded. Franceschetti *et al* published their trial in Italian[13] as well as in English[14], only the latter publication was used. The 30 publications consisted of 18 studies about the effectiveness of AED-prophylaxis, four editorials[15–18], one review-article[2], five studies[12,19–22] mainly concerning the incidence of postoperative epilepsy and two studies[1,23] regarding optimal prophylactic AED-regimes. In these latter two, conclusions were drawn concerning the effectiveness of prophylactically used AEDs, although neither one of them used control-groups. In five of the 18 publications, about the effectiveness of AED-prophylaxis, no control-group was used[11,24–27].

The remaining group of 13 publications was further reduced to eight because some studies were published more than once[28–30].

Three[5,3,31] of the seven studies included patients with neurotrauma. The studies of North *et al*[5] and Lee *et al*[3] were included because data of the ineligible traumatic patient-groups could be separated from the data of the atraumatic part of the patient-population. Four studies[4,14,32,33] described also patients who had experienced preoperative seizures. Two of these, Franceschetti *et al*[14] and Matthew *et al*[4], could eventually be used because the patient-group with preoperative seizures could be separated from the patient-group without preoperative seizures. With the study of Sbeih *et al*[33] however, this was impossible, and for this reason the study was excluded.

The results of the criteria based meta-analysis are shown in Table 2.

Only half of the trials made an inventory of the side-effects of the administered AED-therapy. Usually, there are three different kinds of postoperative seizures defined, depending on the time of onset after the operation. The 'immediate-onset' type occurs within 24 hours, the 'early-onset' within seven days and the 'late-onset' in a period after one week. In three studies[5,34,35] the follow-up took longer than one year. One study[14] had a follow-up of minimal six months and two[3,4] of one week or less (three days). In the studies of Lee *et al*[3] and Matthew *et al*[4] the effectiveness of AEDs preventing post-operative convulsions of the 'immediate-onset' type was investigated.

Scoring on different criteria was affected by a short follow-up, especially with the study of Lee *et al*[3], favouring a good validity.

In one case[14] the baseline characteristics of the control and intervention-group were so sparsely described that less then the minimum score of three points was assigned.

In two publications the data were presented in

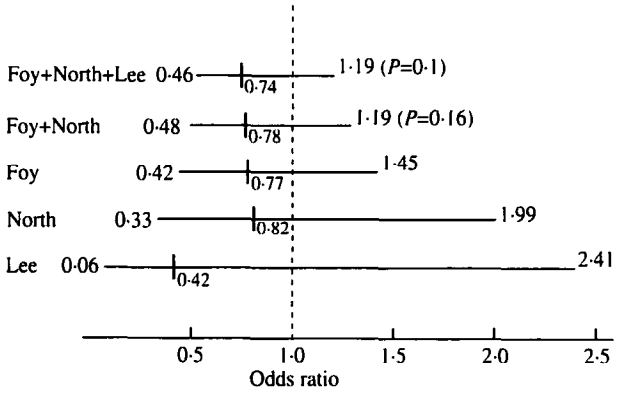

Fig. 1: Odds ratios and confidence intervals (95%) of three statistical analyzed studies: Foy *et al*[34], North *et al*[5] and Lee *et al*[3]. If the confidence-interval (horizontal line), does not cross the vertical line (odds ratio is 1) then the difference in occurence of postoperative convulsions between prophylactic AEDs and placebo can be considered as statistical significant ($P \leq 0.025$ *one-tailed*).

Table 2: Results of the criteria based meta-analysis. Total score is presented as a percentage of the maximum of 145 points, indicating the methodological quality of the study

Author	Foy *et al* (1992)	North *et al* (1983)	Boarini *et al* (1985)	Franceschetti *et al* (1990)	Lee† *et al* (1989)	Matthew‡ *et al* (1980)
Internal validity						
Comparability of prognosis						
Homogeneity (10)*	10	6	6	5	7	6
Prestratification (3)	3	3	-3	-3	3	-3
Randomization (10)	10	10	0	10	10	0
Randomization procedure described (3)	3	0	0	0	3	0
Comparability of relevant baseline characteristics shown (5)	5	5	5	3	5	0
Patients per group (x): $x \leq 50$, $50 < x \leq 100$, $x > 100$ (3/5/7)	5	5	3	3	5	3
Percentage of patients lost to follow-up: $\leq 20\%$ (4) $\leq 10\%$ (7)	7	7	0	0	7	0
Intervention and external variables						
Plasma-levels of anti-epileptics adequate (15)	8	12	5	3	9	0
Dose anti-epileptics adequate (3)	3	3	0	3	3	0
Compliance (4)	4	2	0	0	2	0
Intervention procedures adequately described (10)	7	10	5	6	10	2
Effect measurement						
Patients blinded (10)	0	7	0	0	7	0
Evaluator blinded (5)	0	5	0	0	5	0
Check-up blinding (2)	0	0	0	0	0	0
Proper and relevant outcome-measures						
Remark on side-effects (7)	7	7	0	7	0	0
Remark on difference of seizure-frequency between groups (10)	10	10	10	10	10	10
Remark on type of postoperative convulsions (5)	0	5	5	5	5	0
Follow-up in months after treatment (3/7/9)	9	9	7	7	3	3
Analysis						
Data presentation (5)	5	5	3	3	3	1
Intention-to-treat analysis (5)	5	5	3	3	3	1
Description of methods of analysis (5)	5	5	0	0	0	0
Influence of confounding variables minimized (multi-variate analysis) (5)	5	5	5	0	5	0
Total score (percentage of max. 145)	76.6	87	37.2	44.8	72.4	15.9

* Maximum scores are shown behind each methodological item.
† Follow-up is 3 days.
‡ Follow-up is 1 week.

such a way that simple statistical calculations could be performed[5,35]. These two studies also used the intention-to-treat principle in contrast to the other studies. The most important characteristics of the various publications included in the meta-analysis are shown in Table 3.

Statistical analysis

The three studies selected (methodological quality score ≥55%) for further statistical analysis were: Foy *et al*[35], North *et al*[5] and Lee *et al*[3]. In the trials of North and Lee, ***the trauma capitis group could be separated and excluded from further statistical analysis.*** For the studies mentioned, the odds ratios and their 95% confidence intervals were calculated and pooled, using the Mantel–Haenszel Estimator[10].

On account of the fact that the trial of Lee *et al*[3] only had three follow-up days, and was therefore less comparable to the other two, the studies of North *et al*[5] and Foy *et al*[35] were also pooled without the study of Lee *et al*[3].

The results are presented in Fig. 1.

DISCUSSION

In spite of an extensive literature search, only 30 publications were found on the effectiveness of prophylactic AEDs. After exclusion of trials

Table 3: Most important characteristics of the six valid controlled studies included in the meta-analysis

	Foy *et al* (1992)	North *et al* (1983)	Boarini *et al* (1985)	Franceschetti *et al*(1990)	Lee *et al* (1989)	Matthew *et al* (1980)
Trial-design	Prospective	Prospective	Retrospective	Prospective	Prospective	Retrospective
Main pathology	Aneurysm, AVM, abscess, spont. haematoma, meningioma, benign tumors	Aneurysm, meningioma, metastasis, sellar tumor, glioma, VA shunt, other	Supratentorial astrocytomas	Supratentorial neoplasms	Various pathology	Various pathology
Population size	276	181[5]	68	63[6]	164[5]	87[6]
Score for methodology (% of 145)	76.6	87	37.2	44.8	72.4	15.9
Antiepileptic prophylaxis	Carbamazepine or Phenytoin	Phenytoin	Phenytoin or Phenobarbital or a combination of both	Phenobarbital or Phenytoin	Phenytoin	Phenytoin or a combination of Phenytoin with Phenobarbital or Carbamazepine or Primidone
Period of prophylactic AED intervention	6 or 24 months	12 months	Untraceable in publication	Untraceable in publication	3 days	Untraceable in publication
Period of follow-up	min. 3 years and max. 8 years	24 months	min. 2 months and max. 52 months	min. 6 months	3 days	1 week
Moment of intervention	max. 24 hours before operation	In the recovery-room	max. 24 hours before operation	1 week preoperatively	Shortly before operation	Before operation
Statistical significance of result	No	Yes[1]	No	No	No[4]	No
Author concludes that prophylactic anti-epileptics are useful	No	Yes	?[3]	Yes[2]	?[3]	Yes[2]

(1) Only between day 7 and 72 and including a traumatic patient-population in the statistical analysis. (After leaving out the traumatic patients there was no statistical significant difference between intervention and control-group).
(2) At prevention of Immediate/early-onset seizures but not of Late-onset seizures.
(3) To the authors opinion more investigation is necessary.
(4) After leaving out the traumatic patients there was no statistical significant difference between intervention and control-group.
(5) After substraction of the head trauma population.
(6) After substraction of the population of patients with preoperative seizures.

published twice or more, review articles, trials without a control-group etc., only six clinical trials could be used for a meta-analysis.

After a methodological scoring, three publications remained with a sufficiently high methodological quality; the studies of Foy *et al*[35], North *et al*[5] and Lee *et al*[3] with scores of respectively 76.6%, 87% and 72.4%.

Ultimately only one study remains, Foy *et al*[35], without traumatic patients and/or a too restricted follow-up period. These investigators conclude that AEDs should not be given prophylactically, because a statistically significant difference in outcome was not found.

The effect of the intervention depends on the quality of the antiepileptic prophylaxis reached. An AED is supposed to work optimally if the plasma-levels are within the therapeutic range. Because of this the value of a conclusion about the effectiveness of the intervention is strongly associated with the criterion 'Plasma-levels anti-epileptics adequate'. To define whether an epileptic seizure is the consequence of sub-therapeutic levels, and/or non-compliance, it is of great importance, especially with long term follow-up, to check plasma-levels regularly. This should be done both in the control- and intervention-group to guarantee patient-blinding.

In some of the studies[4,14,34] it appears to be a serious problem to achieve therapeutic plasma-levels in patients. Most of the time it concerns the AED phenytoin which has complicated non-linear pharmacokinetics. Just in the first few days after a craniotomy prevention of postoperative seizures is very important because in this period most of the epileptic seizures (immediate onset-type) occur[17,20,21]. Generally it takes roughly five times the half-time of an AED to reach steady-state pharmacokinetics[36]. With phenytoin ($T_{\frac{1}{2}}$ = 14–31 hours[36,37]) it takes about one week.

In future trials it might therefore be useful to start AEDs seven days before elective neurosurgery in order to achieve adequate plasma-levels at the time of operation. In this way possible acute side-effects of the drug, which can appear during the loading-up period perioperative, can not complicate the postoperative condition of the patient.

However, the amount of blood loss during the operation, which can be extensive with for example meningiomas, affects the postoperative AED-level and should be corrected for.

Because the postoperative incidence of seizures differs quite a lot depending on the patients' pathology[20,21,24], prestratification of the patient-population is very important. These differences in pathology complicate a meta-analysis by reducing the comparability of different studies. In this meta-analysis for example the trial of Boarini *et al*[34] and of Franceschetti *et al*[14] concern a specific pathology, namely gliomas. The incidence of postoperative seizures in patients with gliomas differs from that of patients with another intracranial pathology[20,21,24]. Moreover, in glioma-patients it is difficult, certainly with longer follow-up periods, to differentiate between post-operative seizures caused by the surgical trauma or seizures caused by recurrence of the tumor. A reduction of the diversity of prognostic factors, especially the influence of the patients pathology, could be achieved by including only patients whose pathology gives rise to a high incidence of postoperative seizures[5,27,35].

After calculation of the ORs of the studies of sufficient methodological quality (Foy, North, Lee), it could be determined that in none of these was a statistically significant effect achieved, although in all three studies a trend existed for AEDs to reduce the incidence of postoperative seizures (OR respectively: 0.77, 0.82, 0.42; see Fig. 1). The ORs of these three were subsequently pooled using the Mantel–Haenszel Estimator, but even then statistical significance could not be reached.

Even after pooling, the confidence intervals remained fairly wide. Therefore it is hard to say if the slight tendency of AEDs to prevent post-operative seizures, as deduced from statistical analysis, is of clinical importance. In the statistical analysis no distinction was made between immediate, early and late onset seizures because of the sparsity of data. In order to increase the power to detect a relevant treatment difference it is essential to enlarge the patient-population investigated. Narrowing of confidence intervals leading to a possible statistical significance can be obtained by a large multi-centre trial. Such a multi-centre trial has the advantage of quicker patient accrual, combined with reliable and more representative conclusions to be reached at a faster rate. Disadvantages are the organizational, logistic problems and high cost of large multi-centre trials.

So the question can be raised whether the present prophylactic AED-use is that much harmful and disadvantageous to the patient, that empirical data, proving their effectiveness, must be obtained by means of a high cost and effort multi-centre trial.

The decision to give prophylactic AEDs depends not only on its efficacy but also on factors such as adverse side-effects, discomfort to the patient and costs of the medication. In the publications studied here, only sparse attention was given to the latter factors.

This is disappointing, given the fact that side-effects are often an important argument against the prophylactic use of AEDs. It seems that the conclusions in the studies concerning the use of AEDs were made solely on basis of trial-outcome determining drug efficacy. Especially given the absence of statistical significance of the AED-prophylaxis in these studies, the importance of side-effects, discomfort to the patient and costs of medication beside therapeutic efficacy, should be taken into account, and more carefully examined. Also the use of modern AEDs, with possibly fewer side-effects and shorter loading-up period, should be investigated in any new studies.

Studying the effectiveness of AED-prophylaxis, the type and severity of convulsion should also be taken into account; part of the effectiveness of the AED-prophylaxis may encompass a decrease in severity of a seizure. Of paramount importance in deciding on the use of prophylactic AEDs remains nevertheless its clinical therapeutic effect.

In conclusion, no empirical data supporting the attitude of using AEDs prophylactically with

supratentorial intracranial surgery, have been presented on a scientific basis.

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