British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 315–325 315

META-ANALYSIS

Efficacy and safety of prophylactic levetiracetam in supratentorial brain tumour surgery: a systematic review and meta-analysis

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Received 6 December 2015; **revised** 5 February 2016; **accepted** 2 March 2016

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Keywords brain tumour, levetiracetam, meta-analysis, prophylaxis, seizures, systematic review

AIMS

The aim of this study was to perform an up-to-date systematic review and meta-analysis on the efficacy and safety of prophylactic administration of levetiracetam in brain tumour patients.

METHOD

A systematic review of studies published until April 2015 was conducted using Scopus/Elsevier, EMBASE and MEDLINE. The search was limited to articles reporting results from adult patients, suffering from brain tumour, undergoing supratentorial craniotomy for tumour resection or biopsy and administered levetiracetam in the perioperative period for seizure prophylaxis. Outcomes included the efficacy and safety of levetiracetam, as well as the tolerability of the specific regimen, defined by the discontinuation of the treatment due to side effects.

RESULTS

The systematic review included 1148 patients from 12 studies comparing levetiracetam with no treatment, phenytoin and valproate, while only 243 patients from three studies, comparing levetiracetam vs phenytoin efficacy and safety, were included in the meta-analysis. The combined results from the meta-analysis showed that levetiracetam administration was followed by significantly fewer seizures than treatment with phenytoin (OR = 0.12 [0.03–0.42]: $\chi^2 = 1.76$: $I^2 = 0\%$). Analysis also showed significantly fewer side effects in patients receiving levetiracetam, compared to other groups ($P < 0.05$). The combined results showed fewer side effects in the levetiracetam group compared to the phenytoin group (OR = 0.65 [0.14–2.99]: $\chi^2 = 8.79$: $I^2 = 77\%$).

CONCLUSIONS

The efficacy of prophylaxis with levetiracetam seems to be superior to that with phenytoin and valproate administration. Moreover, levetiracetam use demonstrates fewer side effects in brain tumour patients. Nevertheless, high risk of bias and moderate methodological quality must be taken into account when considering these results.

DOI:10.1111/bcp.12926

Introduction

Brain tumour surgery might be implicated in the occurrence of early or late seizures [1]. Commonly, early seizures appear within the first postoperative week and are attributed to the immediate post-traumatic effect of the surgical procedure as oedema, inflammation or oxidative stress [2]. Conversely, late seizures present beyond the first week after surgical intervention and constitute actual epilepsy [3]. The development of postoperative epilepsy, after supratentorial craniotomy for brain tumour biopsy of excision, has an adverse impact on postoperative clinical course and neurological outcome, cost of hospitalization, and rehabilitation [4]. Thus, the control of perioperative seizures is of utmost importance for outcome optimization in this population.

Although, the treatment of epilepsy related to brain tumours is indisputable, the prophylactic use of antiepileptic drugs (AEDs) for attenuating the risk of postoperative seizures is controversial and the benefits should outweigh the risks associated with the administration [5, 6]. Hepatic enzyme induction, mainly that of cytochrome P_{450} (CYP), is a common side effect of older AEDs, such as phenytoin (PHT), carbamazepine (CBZ) and phenobarbital (PB), while the most prominent adverse effects of valproic acid (VAL) are hepatotoxicity and thrombocytopenia [7–10]. Despite the numerous reports of possible adverse effects, PHT still constitutes the AED of choice for seizure control in most clinical settings [11].

On the other hand, new generation AEDs seem to have an improved safety profile, at least on major complications. For instance, oxcarbazepine (OXC), has minor impact on CYP enzyme induction, but it still can be complicated by hyponatremia and dermatological reactions [12]. Levetiracetam (LEV) has gained popularity mainly due to its unique features in terms of mechanism of action, pharmacokinetics and metabolism [13–15]. A growing body of evidence supports the safety and efficacy of LEV compared to other AEDs in various clinical settings [16, 17]. Despite the fact that several investigators suggest switching from older AEDs to LEV in brain tumour surgery, the evidence for applying LEV as a single agent for perioperative prophylaxis from seizures in brain tumour patients is limited [18–20]. In order to investigate the efficacy and safety of LEV as first-line perioperative prophylactic treatment for seizures, a systematic review and meta-analysis were performed. The study included all published randomized and observational studies of LEV, alone or compared with other AEDs, used in patients with brain tumour undergoing neurosurgical interventions.

Methods

Protocol and registration

A systematic review and meta-analysis for studies testing the efficacy and safety of LEV in patients that underwent craniotomy for supratentorial brain tumours were conducted. The recommendations of the PRISMA statement for reporting Systematic Reviews and Meta-analyses were followed throughout the review process. A protocol was designed before the review started, with registration number PROSPERO 2014:CRD42014013498, and can be accessed at PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013498).

Eligibility criteria

Types of studies. All type of studies (including randomized-controlled studies, non-randomized studies, prospective cohort studies, retrospective studies and case series), were eligible for inclusion. No language or publication date restrictions were imposed.

Types of participants. Patients over 18 years of age, suffering from brain tumour, undergoing supratentorial craniotomy for tumour resection or biopsy and administered LEV in the perioperative period for seizure prophylaxis, were included in this study. Exclusion criteria were patients under the age of 18, pregnancy, breast-feeding, severe co-morbidities (including renal and liver failure) and craniotomy for disease other than brain tumour.

Types of interventions. Studies that examined LEV administration as seizure prophylaxis in patients who underwent supratentorial craniotomy for brain tumour were eligible for inclusion. Furthermore, articles comparing LEV administration to no antiepileptic drug, placebo or other drug were also included.

Types of outcome measures. Primary outcome measures were the efficacy and the safety of LEV. Efficacy was defined either by the appearance or not of seizures or the reduction in the incidence of seizures during the study period. Safety was defined by the reports of side effects (severe, moderate and zero), which were directly attributable to LEV. A secondary outcome measure was the tolerability of the specific regimen, defined by the discontinuation of the treatment due to side effects.

Systematic search

The literature search was conducted in MEDLINE, EMBASE, Scopus/Elsevier, The Cochrane Central Register of Controlled Trials (CENTRAL) and The International Web of Science databases up to 20 February 2014. Additional search was conducted on 20 March 2015. Also, the reference lists of the retrieved articles were searched for further relevant studies. The search was limited to articles reporting results from adult patients. The search strategy is presented in Appendix 1. Based on the search strategy, all titles and abstracts retrieved were independently scanned by two authors (CP, GT). Eligibility of each article retrieved was firstly assessed from the title or the abstract. If eligibility could not be ascertained from the title or the abstract, the full text of the study was retrieved and searched. The article was included for review if eligibility criteria were met, as judged by both authors. In case of disagreements between the two reviewers, the discrepancy was resolved by consulting a third author (DK).

Data collection

A data collection sheet was created and included articles were assessed for:

1 Study design,
2 Total study duration,
3 Risk of bias (randomization if any, sequence generation, allocation sequence concealment, blinding, other concerns about bias),
4 Total number of participants,
5 Setting where the administration of the drug took place (in-hospital or outpatient basis),
6 Diagnostic criteria for seizures (clinical observation or EEG),
7 Age of participants,
8 Sex of participants,
9 Tumour type,
10 Location,
11 Co-administration of corticosteroids,
12 Number of different intervention groups (LEV, placebo, other AED),
13 Route of administration,
14 Dose regimen,
15 Duration of administration,
16 Incidence of side effects in the preoperative or postoperative period (somnolence, nausea/vomiting, headache, insomnia or other rare side effect),
17 Treatment discontinuation due to side effects,
18 Incidence of seizures preoperatively,
19 Incidence of seizures postoperatively.

Preoperative period was defined from the commencement of the treatment until the time of the surgical operation. Postoperative period was further divided into three periods and assessed separately: early postoperative period (the first 48 hours after completion of operation), late postoperative period (48 hours postoperatively–4 weeks postoperatively), late observation period (4 weeks postoperatively–completion of the protocol). Values provided as percentages were converted into actual patient numbers for analysis.

Statistical analysis

The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for the categorical variable. OR < 1 favoured LEV and OR > 1 favoured PHT. Forest plots were used to graphically display the results of the meta-analysis. The random effects model described by DerSimonian and Laird was used to combine the results from the studies [21]. This model calculates a weighted average by incorporating within-study and between-study variations. The Mantel–Haenszel method (fixed effect model) was also used to assess the effect of model assumptions on our conclusions, depending on study heterogeneity [22].

Between-study heterogeneity was assessed with the Cochrane Q test using a χ^2 function (P values < 0.10 were considered significant). In addition, I^2 values were calculated to estimate inconsistency across studies. I^2 values of 25% or less may represent low heterogeneity, values around 50% may represent moderate heterogeneity, and values of 75% or more may represent high heterogeneity. An I^2 value $> 25\%$ was considered significant in this meta-analysis.

Where no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the pooled OR estimates for the remaining studies. All analyses were conducted using RevMan 5.3.

Risk of bias was assessed as described by the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. We assessed the risk of bias in sequence generation, allocation concealment, blinding (including participants and personnel, data collectors, outcome assessors), incomplete data, selective outcome reporting and other sources of bias. Every eligible study was evaluated for any of the above-mentioned risk of bias domains, as having low, high or uncertain risk of bias. All trials that were classified as having low risk of bias, in all of the previously listed domains, were considered as low risk of bias trials. An assessment of reporting biases (such as publication bias) by constructing a funnel plot and using tests for funnel plot asymmetry was planned if there were at least ten studies included in the meta-analysis.

Results

Study selection

A flow chart describing the results of the database and other source search is shown in Figure 1 [24]. Searches returned a total of 1006 records through databases. After removal of duplicates, records were firstly screened by title. Of those, 944 records were excluded as irrelevant and the remaining 62 articles were further screened by abstract. A total of 18 articles were further excluded, based on abstract and the full-text copies of the remaining 44 articles were evaluated for eligibility. Additional searching up to April 2015 revealed one more study eligible for inclusion [25]. Finally, 32 articles were excluded for various reasons, 12 studies met the predetermined inclusion criteria and were subjected to qualitative analysis, and three studies were included in the meta-analysis [18, 25, 26].

Of the 32 full-text articles excluded, four concerned patients under LEV, in which it was impossible to retrieve data regarding safety and efficacy [4, 27–29], three concerned patients under LEV who underwent craniotomy, but data regarding the perioperative period were not described [30–32], four were excluded because patients receiving LEV did not undergo craniotomy [33–36], one study was excluded because patients did not received LEV [37], one was excluded because patients received a combination of LEV with PHT [38] and one study was excluded because the authors enrolled patients under the age of 18 [39].

Furthermore, 18 articles were also excluded because they were reviews, and data regarding LEV efficacy and safety could not be retrieved [11, 40–56]. However, the reference lists of these articles were manually screened for possible eligible publications, but all relevant articles cited were already screened from the database screening process.

Study characteristics

The characteristics of the 12 included studies are shown in Table 1. Among them only one was a randomized controlled study while four were prospective studies and the remaining seven studies were retrospective. Four of them studied the effect of LEV administration without a control group [20, 56–58], one compared LEV with no treatment [59], one

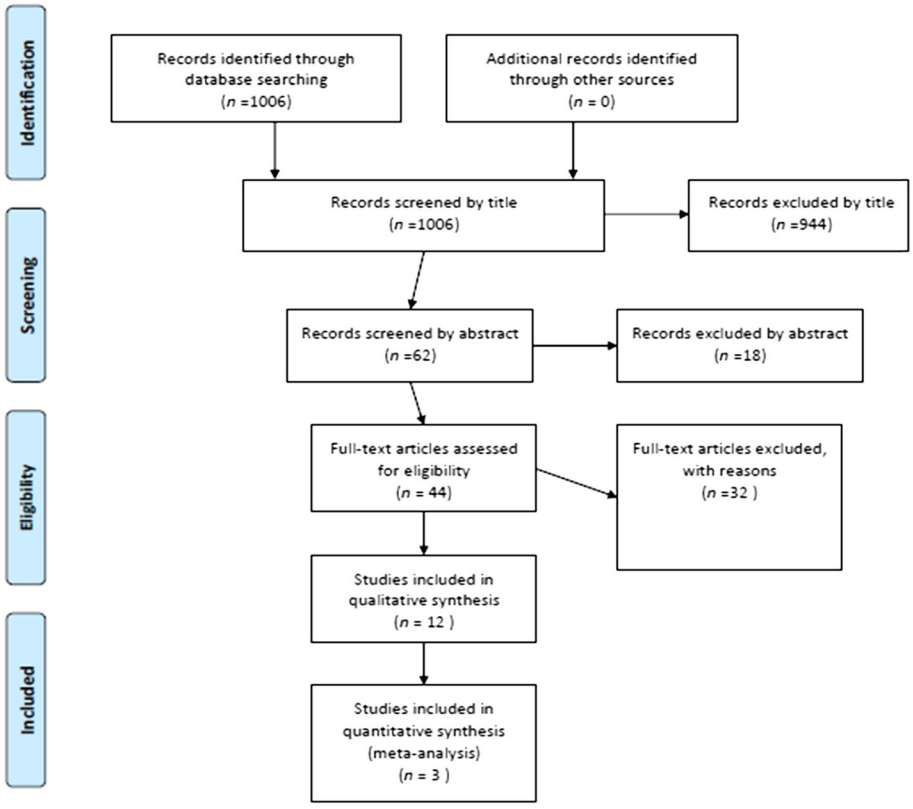

Figure 1
Flow diagram of study selection in the systematic review and meta-analysis of the efficacy and safety of LEV (levetiracetam) prophylactic administration in brain tumour patients [24]

compared LEV with VAL administration [10], while another compared LEV with VAL administration both as adjuvant therapy to Temozolomide (TMZ) [60] and five compared LEV with PHT administration [18, 25, 26, 61, 62]. Ultimately, four of them [18, 25, 26, 62] met the criteria to be included in the meta-analysis.

Participants

A total of 1148 patients were enrolled in 12 studies included in the systematic review. The study conducted by Milligan *et al.* included 315 patients with various intracranial pathologies [61]. However, only data regarding patients with primary brain tumours have been extracted. Hence, a total of 43 and 56 patients with primary brain tumours were treated with LEV and PHT respectively and were finally included in the present analysis. Also, the study conducted by Kerkhof *et al.* included 143 patients, only 72 of whom received LEV or VAL as monotherapy and were finally included in the present study. Moreover, among 1148 patients enrolled, 533 took LEV as monotherapy, 200 took PHT, 267 took VAL and 48 took no antiepileptic therapy (Table 1).

Interventions

Regarding time of outcome assessment, the study period varied from 7 days [25, 58] up to 12 months [57, 61]. Data from the early postoperative period (during the first 48 hours after surgery) could be extracted from only one article [56], while data from 48 hours to 4 weeks postoperatively could be retrieved from eight studies [10, 20, 26, 56, 57, 59, 61, 62]. The late observation period (>4 weeks postoperatively) was terminated at 3 months in one study [26], at 6 months in three studies [18, 59, 60] and at 12 months in two studies [57, 61].

Routes of administration were mentioned in six studies [10, 18, 20, 25, 26, 56]. Most used a combination of intravenous plus oral regimen, depending on patient ability to swallow. LEV administration ranged from 500 to 3000 mg daily [20, 61], from 1000 to 3000 mg daily [25, 57], from 500 to 1000 mg [26], from 1000 to 2000 mg [58–60] and from 2000 to 3000 mg [56]. In most studies dose titration was attempted according to effect. Similarly, PHT administration was guided by serum levels in the study by Lim *et al.* (targeted to serum levels of 10–20 mg dl^{-1}) while Iuchi and colleagues administered PHT starting with a loading dose of 15–18 mg kg^{-1}, followed by an intravenous administration of 5–7.5 mg kg^{-1}/day and then 250 mg daily [18, 25]. The trials conducted by Milligan *et al.* and Merrell *et al.* did not present data regarding PHT dose regimen [61, 62]. Finally, drug administration in the study by Lee *et al.* was targeted to achieve 50–100 μg ml^{-1} serum levels of VAL [10].

Evaluation of effectiveness

Data regarding incidence of seizures during the early postoperative period (first 48 hours postoperatively) could be extracted only from the study by Bahr *et al.*, who reported an incidence of 3/25 for patients receiving LEV [56]. Among

Table 1

Characteristics of the included studies

Source	Study design	Study period	Intervention/control	No of pts	Age	Time of outcome assessment		Side effects
						<4 weeks	4w-12mo	
Bahr *et al.* [56]	Prospective, open-label	4 weeks	LEV po or iv 500 × 2/3d po, then 1000 × 2 In case of seizures up to 1500 × 2	LEV 25	23–78 yrs	6/25 (3/25 48 h postop)		1/25 paresthesia + visual field deficit
Fuller *et al.* [26]	Prospective, open-cohort	3 mo	LEV vs PHT LEV 250–1000 × 2 po or iv PHT 300 × 3 or 1gr iv (loading)- 300 mg/d po or iv	LEV 36 PHT 38	LEV 25–88 yrs PHT 27–89 yrs	LEV 0/36 PHT 6/38 (1/38 48 h postop)		1/25 paresthesia + nystagmus
Gokhale *et al.* [58]	Retrospective	1 week	LEV p.o or i.v. 1000–2000 mg/day	LEV 165	18–82 yrs	12/165 (10 generalized and 2 partial seizures		7/165 somnolence
Garbossa *et al.* [59]	Retrospective 2-centre study	6 mo	LEV vs control (none) LEV 500 × 2/3-5d preop 500 × 2 for 6 mo postop or 1000 × 2 (in case of seizures)	LEV 43 Control 48	LEV 59 47 (SD 12) Control 63.9 (SD 11.8)	LEV 1/43 Control 0/48	LEV 5/43 (3mo) Control 3/48 LEV 2/41 (6 mo) Control 6/45 (6 mo)	LEV 1/43 ataxia
Iuchi *et al.* [25]	randomized, prospective, open-cohort, study	7 days	LEV 500 × 2 sup → po PHT 15–18 mg kg^{-1} iv → 5–7.5 mg kg^{-1}/day iv, then 250 mg po daily	73 LEV 73 PHT		1/73 LEV 11/73 PHT	3/73 LEV (liver dysfunction 8/73 PHT (2 liver dysfunction, 2 hyponatriemia, 2 skin rash, 2 atrial fibrillation)	3/73 LEV liver dysfunction 2/73 PHT liver dysfunction 2/73 PHT hyponatriemia 2/73 PHT skin eruption 2/73 PHT atrial fibrillation
Kerkhof *et al.* [60]	Retrospective	6 mo	LEV vs VAL LEV p.o or i.v. 1000 mg/day (or 2000 mg/day in case of seizures) VAL p.o or i.v. 1000 mg/day (or 2000 mg/day in case of seizures)	LEV 36 VA L36	24–85 yrs		LEV 8/36 VAL 11/36	LEV 1/36 severe fatigue + allergic reaction

(Continues)

Table 1

(Continued)

Source	Study design	Study period	Intervention/control	No of pts	Age	Time of outcome assessment <4 weeks	Time of outcome assessment 4w-12mo	Side effects
Lee *et al.* [10]	Retrospective	4 weeks	LEV vs VAL	LEV 51/282	LEV 50.6 (SD 16.6)	LEV 4/51		Total LEV 5/51
			LEV 500 × 2 iv (preop-1st postop days)	VAL 231/282	VAL 50.9 (SD 17.3)	VAL 15/231		VAL 62/231
			LEV 500 × 2 1500 × 2 (in case of seizures)					
			VAL 600 mg for 12 h preop					
			VAL 50 mg for 24 h 1st postop					
			VAL 600 mg × 2 titration to serum levels					
Lim *et al.* [18]	RCT	6 mo	LEV vs PHT (0 postop)	LEV 15	LEV 20–56		LEV 2/15	LEV 0/15
			LEV 1000 × 2 iv + tapering off PHT up to POD3	PHT 8	PHT 32–83		PHT 2/8	PHT 3/8 difficulty in coordination
			PHT 300-400 mg × 1 according serum levels				6 mo evaluation	
Merrell *et al.* [62]	Retrospective	4 weeks	LEV vs PHT	LEV 51	LEV 25–77	LEV 2/51		LEV:3/51
			NR	PHT 25	PHT 32–79	PHT 5/25		PHT5/25
Milligan *et al.* [61]	Retrospective	12 mo	LEV vs PHT	LEV 105	Primary brain tumour	LEV 1/43	LEV 5/11	
			LEV 500–3000 mg/d (1000 mg)					
			PHT 200–800 mg/d (300 mg)	PHT 210	LEV 43/105	PHT 2/56	PHT 24/44	
					PHT 56/210			
Usery *et al.* [20]	Prospective	4 weeks	LEV 500 × 2 iv → po	LEV 20	LEV 27–77	LEV 1/17		3/17 somnolence
			Titrated 500 mg per day					1/17 nausea/ vomiting
								1/17 headache
			Up to 3000/d					1/17 insomnia
Zachenhofer *et al.* [57]	Retrospective	12 mo	LEV 500 × 2 iv or 500 × 3	LEV 78	LEV 27–89	LEV 2/78 (7 days)	LEV 7 (whole 180 days)	3/78 somnolence
			Titrated up to 3000/d			5/78 (4 weeks)		2/78 psychosis

LEV, levetiracetam; mo, months; PHT, phenytoin; postop, postoperatively; SD, standard deviation; VAL, valproate; yrs, years

studies evaluating incidence of seizures during the late postoperative period, the combined incidence of seizures was 41/533 for the LEV group (7.69%) [10, 20, 25, 26, 56–59, 61, 62]. Regarding PHT patients, the combined incidence of seizures during the late postoperative period was 22/192 (11.5%). Only two studies included patients under VAL [10]. The authors showed an incidence of seizures up to 4 weeks postoperatively in 26/267 patients (9.73%) under VAL therapy. The only study that used no treatment as a control demonstrated no seizures, among 48 patients, during 4 weeks postoperatively (0/48) [59]. For the late observation period, 25/168 patients under LEV experienced seizures (14.9%), compared to 26/52 (50%) under PHT. Moreover, among patients receiving no treatment, only 6/48 had seizures (12.5%).

Three studies, enrolling 243 patients in total and comparing LEV with PHT effectiveness, were included in the meta-analysis [18, 25, 26]. Due to the small number of trials included, it was not possible to extract data regarding the incidence of seizures through different study periods (first 48 hours, late postoperative period, late observation period). The combined results from these three studies showed that LEV administration was followed by significantly fewer seizures than with PHT (OR = 0.12 [0.03–0.42]: χ^2 = 1.76: I^2 = 0%, see Figure 2).

Side effects

Considering the combined incidences of side effects, a total of 55/533 (10.3%) patients under LEV were recorded to have had at least one side effect, while the combined incidences for PHT and VAL were 45/200 (22.5%) and 62/267 (23.2%) respectively (Table 1). Analysis showed significant fewer side effects in patients receiving LEV, compared to other groups ($P < 0.05$). Three studies comparing LEV with PHT were included in the meta-analysis. The combined results showed fewer (but not statistically significant) side effects in the LEV group, compared with the PHT group (OR = 0.65 [0.14–2.99]: χ^2 = 8.79: I^2 = 77%, Figure 3). A sensitivity analysis was conducted, and the pooled OR was not significantly changed when individual studies were removed each in turn (Figure 3).

Risk of bias estimation

We assessed the risk of bias in sequence generation, allocation concealment, blinding (including participants and personnel, data collectors, outcome assessors), incomplete data and selective outcome reporting and other sources of bias (Table 2). Most of the studies enrolled are characterized by high risk of bias, due to the absence of data regarding randomization technique or blinding. Only the study conducted by Fuller *et al.* is characterized by proper randomization and blinding [26]. However, data regarding patient blinding are missing. Publication bias analyses were not pursued because the number of studies included in the meta-analysis was insufficient and when there are fewer than ten studies, the power of the tests is too low to distinguish chance from real asymmetry.

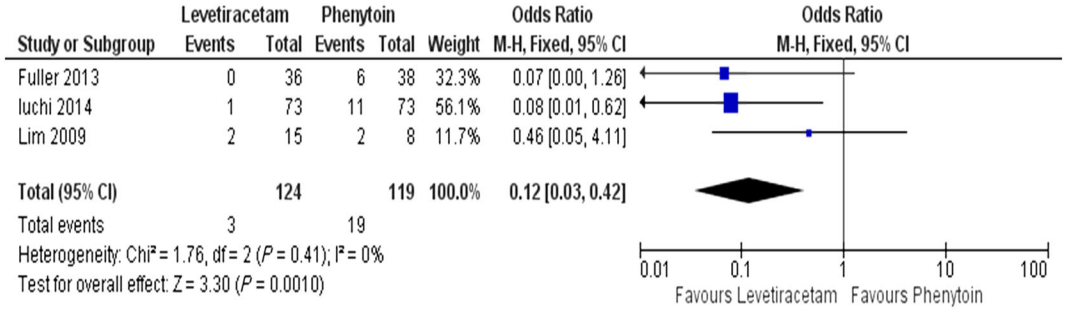

Figure 2

Forest plots and pooled odds ratio (OR) measures with 95% confidence interval (CI) for categorical variable of LEV (levetiracetam) and PHT (phenytoin) postoperative seizures. M-H: Mantel–Haenszel method (fixed effect model)

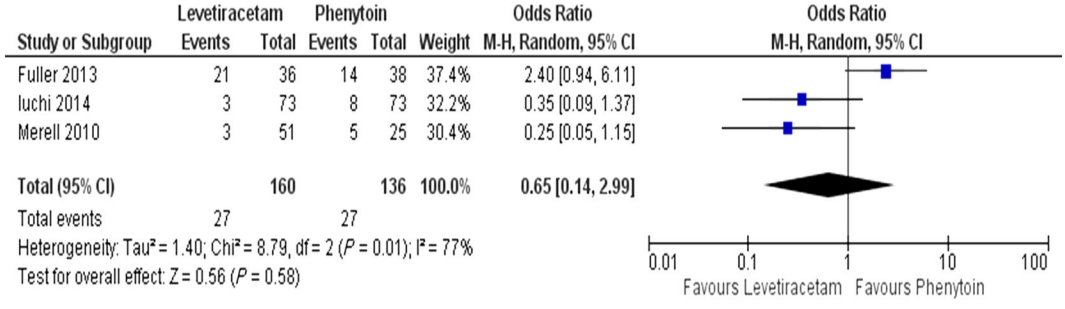

Figure 3

Forest plots and pooled odds ratio (OR) measures with 95% confidence interval (CI) for categorical variable of LEV and PHT side effects. M-H: Mantel–Haenszel method (fixed effect model)

Table 2

Risk of bias of the included studies

Source	Sequence generation	Allocation concealment	Patients blinded	Personnel blinded	Data collectors blinded	Outcome assessors blinded	Incomplete outcome data	Selective reporting	Summary
Bahr *et al.* [56]	No	No	No	No	No	No	Low	Low	High
Fuller *et al.* [26]	No	No	No	No	No	No	Low	Low	High
Gokhale *et al.* [58]	No	No	No	No	No	No	Low	Low	High
Garbossa *et al.* [59]	Low	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Iuchi *et al.* [25]	Low	Low	No	No	No	No	Unclear	Unclear	High
Kerkhof *et al.* [60]	No	No	No	No	No	No	Low	Low	High
Lee *et al.* [10]	No	No	No	No	No	No	Low	Low	High
Lim *et al.* [18]	Unclear	Unclear	No	No	No	No	Low	Low	High
Merrell *et al.* [62]	No	No	No	No	No	No	Low	Low	High
Milligan *et al.* [61]	No	No	No	No	No	No	Low	Low	High
Usery *et al.* [20]	No	No	No	No	No	No	Unclear	Unclear	High
Zachenhofer *et al.* [57]	No	No	No	No	No	No	Unclear	Unclear	High

Discussion

In the systematic review, the efficacy and safety of LEV in patients who underwent supratentorial craniotomy for brain tumour resection was examined. Studies investigating LEV administration versus other AEDs and LEV versus no therapy were included, as well as studies investigating LEV treatment without a control group. Due to the very limited number of randomized controlled trials (RCTs) evaluating LEV administration, it was decided to also include non-randomized prospective and retrospective studies in the eligibility criteria. A recently published systematic review by the Cochrane Collaboration evaluated different antiepileptic drugs administered pre- or post-operatively as prophylaxis for post-craniotomy seizures in patients being operated for various central nervous system pathologies and not exclusively brain tumour patients [63]. Although the study design of this systematic review included only randomized controlled studies, the notable heterogeneity among them ruled out the possibility of a further meta-analysis. Moreover, Yuan *et al.* published a meta-analysis in order to evaluate only efficacy and not safety of LEV in patients with brain tumours [64]. They included studies with significant heterogeneity in study design as well as in intervention groups, leading to results requiring caution in clinical interpretation. To our knowledge the present study is the only systematic review combined with meta-analysis that examines both efficacy and safety of prophylactic use of LEV in patients with brain tumours.

Based on our eligibility criteria, we included four studies examining LEV administration without comprising a control group in their study design [20, 56–58]. The reported incidence of seizures during the study period was relatively low, ranging from 5.9% [20] to 25% [56]. Similarly, a rather limited risk of side effects was identified, ranging from 3.8% [57] to 35.3% [20]. However, these can be considered as low quality studies, as two of them are retrospective studies, and the other two, although being prospective, involve a rather limited number of participants, raising questions about the efficacy and safety of prophylactic use of LEV.

Only one study compared LEV administration with no treatment as a control group, in patients undergoing craniotomy for brain tumours [59]. In this retrospective, two-centre study, the authors evaluated the effect of perioperative LEV administration (starting 3–5 days preoperatively and continued up to 6 months after surgery), compared to a control group, in which no perioperative antiepileptic treatment was administered. The authors found that LEV prophylaxis was not a significant predictor of seizure occurrence, although the regression analysis indicated a slight reduction in seizure risk following LEV administration. Furthermore, the 30-day incidence of seizures after surgery was extremely low (2.4% for the LEV group versus 0% for the no treatment group), while, regarding side effects, only one case of ataxia was recorded among patients.

One retrospective study compared LEV with VAL administration in craniotomy patients [10]. The authors examined antiepileptic therapy starting 24 hours before operation, at doses 500 mg twice a day for LEV and 600 mg for VAL and continuing for 4 weeks postoperatively at doses 500 mg twice a day for LEV (titrated to 1500 twice a day according to seizure activity) and 600 mg twice a day for VAL (titrated to serum levels). As far as efficacy was concerned, they found that the postoperative seizure control rates of LEV and VAL acid were not statistically significantly different. Nevertheless, despite comparable incidence of seizures between groups, the authors concluded that the side effects indicated that the long-term complication rate of the VAL group was significantly higher than that of the LEV group. In the VAL group, 10 cases with hepatic toxicity, 20 cases with hyperammonemia and 10 cases with hematologic disorders were recorded. Switching to other and/or additional anticonvulsants, because of either side effects or uncontrolled seizures, was necessary in 38.5%

of the cases receiving VAL, whereas only nine patients (17.6%) in the LEV group changed treatment.

Among the included studies, five compared LEV with PHT administration [18, 25, 26, 61, 62], but only three of them were eligible, regarding LEV efficacy, for quantitative analysis, so a meta-analysis was conducted [18, 25, 26]. The meta-analysis outlined that LEV was superior to PHT regarding the occurrence of seizures postoperatively. The included studies comprised one RCT [18] and two prospective studies [25, 26], suggesting a moderate quality of evidence. Risk of bias was also considered unclear or high for the included studies.

Another critical issue was the variability of the dose regimens used in the included studies. Despite the low heterogeneity considering efficacy, there was a significant variability of the dose regimens used among the selected studies. Fuller *et al.* used LEV doses ranging from 500 to 2000 mg daily, Lim *et al.* used a standard regimen of 2000 mg and Iuchi *et al.* administered 1000 mg daily [18, 25, 26]. Similarly, PHT administration varied from 300 mg daily in Fuller *et al.* to 300–400 mg daily and 5–7.5 mg kg^{-1}/day iv then 250 mg daily in Lim *et al.* and Iuchi *et al.* respectively [18, 25, 26]. Furthermore, investigators titrated dose regimen according to effect. Consequently it is difficult to conclude about doses in which LEV demonstrates its beneficial effect compared to PHT.

Among studies comparing LEV with PHT administration which were not included in the meta-analysis, Milligan *et al.* found a similar risk for early and late seizures between the two anticonvulsants, but LEV administration was superior to PHT in terms of the occurrence of side effects [61]. Similarly, the study conducted by Merrell *et al.* (not included in meta-analysis), demonstrated comparable occurrence of seizures and side effects between LEV and PHT patients [62]. Both studies had a retrospective design while data regarding dose regimens could not be retrieved from the Merrell *et al.* study [62].

Considering side effects, three studies comparing LEV with PHT administration were subjected to quantitative analysis [25, 26, 62]. The meta-analysis conducted suggested that the rate of side effects was rarer in LEV patients compared to PHT patients (OR = 0.65 [0.14–2.99]: $\chi^2 = 8.79$, Figure 3). However, the included studies are characterized by high heterogeneity regarding side effects: $I^2 = 77\%$. Additionally, among studies comparing LEV with PHT administration which were not included in the meta-analysis, Milligan *et al.* reported 1/43 patients under LEV treatment versus 14/56 under PHT with side effects, while Lim *et al.* reported 0/15 LEV patients compared to 4/8 PHT patients presenting with side effects [18, 61].

Conclusions

In conclusion, few studies examined efficacy and safety of LEV administration in the perioperative period for controlling seizures. Only three studies (one RCT and two prospective studies) that compared LEV with PHT administration could be subjected to quantitative analysis regarding the occurrence of seizures. According to the analysis, LEV administration seems to be more effective in controlling postoperative seizures. Similarly, only three studies comparing LEV with PHT administration could be included in the meta-analysis regarding side effects, demonstrating fewer not statistically significant side effects in LEV patients. Nevertheless, a high risk of bias and moderate methodological quality must be taken into account when considering these results. Consequently, further well-designed studies are necessary in order to confirm the superiority of LEV as prophylaxis for controlling seizures in the perioperative period.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors report no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Appendix 1

Searching strategy, combining free text and medical subject headings (MeSH terms) was set up for PUBMED as follows:

("keppra"[All Fields] OR "levetiracetam"[All Fields]) AND (("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]) OR ("craniotomy"[MeSH Terms] OR "craniotomy"[All Fields]) OR ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "operation"[All Fields]) OR ("brain tumour"[All Fields] OR "brain neoplasms"[MeSH Terms] OR ("brain"[All Fields] AND "neoplasms"[All Fields]) OR "brain neoplasms"[All Fields] OR ("brain"[All Fields] AND "tumour"[All Fields]) OR "brain tumour"[All Fields]) OR ("supratentorial tumour"[All Fields] OR "supratentorial neoplasms"[MeSH Terms] OR ("supratentorial"[All Fields] AND "neoplasms"[All Fields]) OR "supratentorial neoplasms"[All Fields] OR ("supratentorial"[All Fields] AND "tumour"[All Fields]) OR "supratentorial tumour"[All Fields]) OR (("seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields]))).

Searching strategy, using combination of terms was set up for Scopus/Elsevier as follows: TITLE-ABS-KEY (("keppra" OR "levetiracetam") AND (surgery OR craniotomy OR operation OR "brain tumour" OR "supratentorial tumour" OR "seizure prophylaxis")).

Searching strategy, using combination of terms was set up for EMBASE as follows: SUBJECT HEADING: (("keppra" OR "levetiracetam"), USED FOR (surgery OR craniotomy OR operation OR brain tumour OR supratentorial tumour OR seizure prophylaxis)).

Searching strategy, using combination of terms was set up for The International Web of Science as follows: TOPIC: (("keppra" OR "levetiracetam") AND (surgery OR craniotomy

OR operation OR brain tumour OR supratentorial tumour OR seizure prophylaxis)).
Searching strategy, using combination of terms was set up for The Cochrane Central Register of Controlled Trials (CENTRAL) as follows: Levetiracetam, Levetiracetam AND surgery.

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