厚生労働科学研究費補助金（医療技術実用化総合研究事業）
（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

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研究要旨
脳腫瘍患者に対する放射線治療後に生じた症候性脳放射線壊死に対して抗 VEGF 抗体であるベバシズマブの投与を行い、その有効性と安全性を検証する多施設間共同研究に参加した。

A．研究目的
脳腫瘍放射線治療後に生じた症候性脳放射線壊死の治療におけるベバシズマブの臨床効果を検証する。

B．研究方法
大阪医大を中心とする多施設間共同研究体制に入り、策定されたプロトコールに乗っ取り、同意を得た患者にベバシズマブによる治療を施行し、患者のフォローアップを行う。
なお研究分担者は平成25年4月より東北大学医学部脳神経外科・准教授の立場から現職に異動した。本研究の登録症例は東北大学における症例となる。

（倫理面への配慮）
臨床研究プロトコールは東北大学医学部附属病院の倫理委員会によって審議され承認済みである。患者には十分な説明を行い、同意を書面で得た後に研究参加していただいた。

C．研究結果

合計1名の患者を登録した。
以下にその症例の簡単な経過を示す。
症例は2005年5月（27歳）より治療歴のある右前頭葉の退形成性乏突起星細胞腫の再発症例である。2009年11月に再発症例に対して再摘出術後追加化学療法を行っていたが、さらに摘出腔壁の造影領域と両側大脳半球に浸潤するT2/FLAIR高信号領域に対して2012年1月中性子捕捉療法を大阪医大にて行った。その一ヶ月後から急速に造影領域と浮腫の拡大を認め、bevacizumab投与を行った。これにより著しく病態は改善し、通常の生活に戻ることが可能となった。2012. 12. 31までこの状態を維持することを確認後、前述のように北里大学へ異動となった。

D．考察
本臨床試験は症候性脳放射線壊死の治療として適切な治療効果が得られた。また、大きな副作用は認めなかった。

E．結論
今後本臨床試験の結果を集計し、統計処理を行い、薬事承認に備えたい。

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G. 知的所得権の取得状況
1. 特許取得
なし

2. 実用新案登録
なし

3.その他
特記事項なし

研究成果の刊行に関する一覧表
雑誌

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RESEARCH PAPER

Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study

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ABSTRACT

Objective Phenytoin (PHT) is routinely used for seizure prophylaxis in patients with brain tumours during and after craniotomy, despite incomplete evidence. We performed a prospective, randomised study to investigate the significance of prophylactic use of levetiracetam (LEV), in comparison with PHT, for patients with supratentorial tumours in the perioperative period.

Methods Patients were randomised to receive LEV, 500 mg/body every 12 h until postoperative day 7, or PHT, 15–18 mg/kg fosphenytoin followed by 125 mg PHT every 12 h until postoperative day 7. The primary end point was the occurrence of seizures, and secondary end points included the occurrence of haematological and non-haematological adverse events.

Results One hundred and forty-six patients were randomised to receive LEV (n=73) or PHT (n=73). The incidence of seizures was significantly less in the LEV group (1.4%) compared with the PHT group (15.1%, p=0.005), suggesting benefit of LEV over PHT. The observed OR for being seizure free in the LEV prophylaxis group relative to the PHT group was 12.77 (95% CI 2.39 to 236.71, p=0.001). In a subgroup analysis of patients who did not have seizures before craniotomy, similar results were demonstrated: the incidence of seizures was 1.9% (LEV) and 13.8% (PHT, p=0.034), and OR was 8.16 (95% CI 1.42 to 154.19, p=0.015). LEV was completed in all cases, although PHT was withdrawn in five patients owing to liver dysfunction (1), skin eruption (2) and atrial fibrillation (2).

Conclusions Prophylactic use of LEV in the perioperative period is recommended because it is safe and significantly reduces the incidence of seizures in this period.

Trial registration number UMIN13971.

INTRODUCTION

Seizures are a common symptom in patients with supratentorial brain tumour. The frequency of seizures varies with the histological type of tumour, but it is reported that up to 78% of patients with brain tumours experience seizures in their disease course.[1 2] However, four randomised studies[3–6] and six cohort studies[7–12] have revealed that antiepileptic drugs (AEDs) are not effective in preventing initial seizures in patients with newly diagnosed tumours. Based on this evidence, the American Academy of Neurology has published a recommendation that prophylactic AEDs should not be used routinely in patients with newly diagnosed brain tumours.[13]

In contrast, a relatively high incidence of seizures after surgery for supratentorial tumours has been reported,[14 15] and the prophylactic effect of phenytoin (PHT) on prevention of postsurgical seizures has been demonstrated in a prospective double-blind study.[3] In addition to this evidence, PHT is the only AED that can be administered intravenously in Japan. Therefore, this agent is routinely used during and after craniotomy at the majority of hospitals in Japan.

More recently, however, PHT was reported to be the only AED significantly associated with communication problems during awake craniotomy.[16] In the recent treatment of malignant gliomas, 5-aminolevulinic acid (5-ALA)-based intraoperative fluorescence-guided surgery has improved the extent of resection. This treatment depends on tumour-specific accumulation of protoporphyrin IX, which is a metabolite of 5-ALA, but PHT has been reported to reduce this accumulation.[17] These findings indicate that PHT is not the best choice of AED for seizure prophylaxis during and early after craniotomy. Furthermore, a recent randomised prospective study failed to prove the effect of PHT on seizure prophylaxis in patients with brain tumour.[18] In this study, we prospectively compared the effect and risk of levetiracetam (LEV) with PHT for prophylactic use of these agents in the perioperative period (within 1 week after craniotomy).

MATERIALS AND METHODS

Study design

This was a randomised, prospective, open-cohort, single-centre study. Patients with intracranial tumours diagnosed on MRI were enrolled. After enrolment, patients were randomised (1:1) to receive either AED prophylaxis with LEV (group L) or PHT (group P). This individual randomised allocation was performed using sequentially numbered envelopes by one of the investigators (KK). The primary end point of this study was seizure, and the secondary end point was occurrence of side effects as measured during and early after craniotomy. All patients provided written informed consent.

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Eligibility criteria

Eligible patients were aged ≥16 years with supratentorial tumours that required craniotomy, and with adequate renal and hepatic function (creatinine <1.5× upper limit of normal (ULN), aspartate aminotransferase <3× ULN, alanine aminotransferase <3× ULN and bilirubin <1.5× ULN). The history of seizures prior to surgery was not considered, but patients were excluded if they had a history of seizures and their seizures remained after medication with LEV or PHT. For patients who experienced no seizure before surgery, the risk and benefit of prophylactic AEDs were explained, and only the patients who provided informed consent were included. Patients with known allergy to either study medication were also excluded. Other exclusion criteria were solely posterior fossa tumours, pregnancy and colostomy.

Treatment

In patients who had a history of seizures prior to surgery, and who received AEDs to control seizures, AEDs were continued until the day before surgery. In group L, we administered 500 mg LEV after induction of general anaesthesia. LEV was administered by a suppository every 12 h until oral intake became available. Oral LEV was continued until postoperative day 7. In group P, patients received 15–18 mg/kg fosphenytoin (FOS) intravenously after induction of general anaesthesia. Intravenous FOS administration was continued at a dose of 5–7.5 mg/kg/day. After patients were able to take oral medication, 250 mg/day PHT, which was sufficient to achieve a therapeutic plasma concentration in most Japanese patients, was administered until postoperative day 7. The plasma concentrations of AEDs 2 h after the first administration were measured in both groups.

Follow-up

MRI was routinely performed within 48 h after surgery, and was able to detect postoperative complications leading to seizures/side effects. All patients were hospitalised during the whole period of the study and we recorded the appearance of seizures until 7 days after surgery. Any kind of seizures, such as partial, complex partial, tonic–clonic and psychomotor seizures, was recorded regardless of their duration and severity. Blood analysis was performed on the day after surgery and on postoperative day 6 to evaluate the changes in renal and hepatic function. Haematological and non-haematological toxicity was graded according to the Common Terminology Criteria for Adverse Events, V.4.0, to facilitate the comparison of the severities of adverse effects between the two treatment groups.[18]

Statistical analysis

We used Fisher's exact test, χ^2 test and Wilcoxon test to compare patients in the two treatment groups with respect to clinical and demographic factors. Seizure control rates were compared between the two groups by Fisher's exact test, and were also analysed according to the following variables: age (<60 years vs ≥60 years), sex, pathology (glioma vs others), tumour location, type of anaesthesia and duration of surgery (<3 h vs ≥3 h). All parameters were analysed as categorical variables. Univariate and multivariate analyses were performed using a logistic regression model. A p value <0.05 was considered statistically significant. Furthermore, the difference in incidence of seizure between patients treated by LEV and PHT was also evaluated separately in patients without preoperative seizures. All statistical analyses were performed using JMP for Mac V.10.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study population

Between April 2013 and April 2014, 166 craniotomies were performed in our hospital. Nineteen patients with infratentorial tumours were excluded and the remaining consecutive 147 patients were randomly assigned: 74 to receive LEV (group L) and 73 to receive PHT (group P). One patient in group L was excluded from the analysis because his intracranial lesion was pathologically diagnosed as non-neoplastic. Characteristics of the remaining patients in the two treatment groups are shown in table 1, and were well balanced.

Seizure was the first symptom in 23 cases (11 in group L and 12 in group P). In addition to these patients, 13 other patients developed seizures before surgery (10 in group L and 3 in group P). AEDs administrated prior to surgery are also listed in table 1. In 112 cases, no AEDs were administered before surgery. Among the 36 patients with a history of seizure, seizures were well controlled before surgery with AEDs in 27 patients, while the remaining nine patients still exhibited

Table 1 Patient characteristics

	Levetiracetam n=73	Phenytoin n=73	p Value
Female/male (n)	24/49	29/44	0.491*
Age (year)	57 (21–88)	60 (17–88)	0.936†
Pathology (n)			0.159‡
Glioma	44	31	
(Grade I/II/III/IV)	(3/6/6/29)	(0/9/3/19)	
Metastasis	23	31	
Meningioma	2	5	
Others	4	6	
Region			0.909‡
Frontal	28	27	
Temporal	19	17	
Parietal	12	12	
Occipital	9	10	
Deep brain	4	7	
Maximum diameter	39.7 (14.0–79.8)	35.0 (9.3–66.1)	0.110†
Seizure before surgery (never/controlled/intractable)	52/16/5	58/11/4	0.504‡
AED prior to surgery			0.190‡
Carbamazepine	5	2	
Valproate	4	3	
Phenytoin	0	3	
Phenobarbital	0	1	
Levetiracetam	9	4	
Lamotrigine	1	1	
Zonisamide	0	1	
No	54	58	
Anaesthesia (n)			0.451*
General anaesthesia	62	66	
Awake surgery	11	7	
Duration of surgery (min)	202 (53–380)	185 (50–149)	0.126†
Severe oedema after surgery (yes/no)	10/63	8/65	0.802*

*Fisher's exact test.
†Wilcoxon test.
‡χ^2 test.
AED, antiepileptic drug.

seizures after administration of AEDs. We expressed the status of seizure at craniotomy as follows: 'never' for patients who never experienced a seizure at all; 'controlled' for patients with a history of seizures but well controlled by AEDs; and 'intractable' for patients who still exhibited seizures after administration of AEDs.

Seizure prophylaxis

The average plasma concentrations of LEV and PHT 2 h after administration of these agents were 9.4±3.7 (SD) μg/mL and 9.9±2.9 (SD) μg/mL, respectively.

No seizure was observed during surgery in any patient, including 18 with awake craniotomy (11 in group L and 7 in group P). After surgery, 12 patients developed seizures: on the day of surgery in six, the day after surgery in two, 2 days after surgery in two, 5 days after surgery in one and 6 days after surgery in one. The incidence of seizures in group L (1.4%) was significantly lower than that in group P (15.1%, p=0.005). The use of PHT had a higher risk of postsurgical seizures compared with LEV (OR 12.77; 95% CI 2.39 to 236.71; p=0.001). Among these 12 seizures, five were tonic–clonic and the remaining seven were partial seizures. All of the tonic–clonic seizures were observed in group P (6.9%). The use of PHT also had a higher risk of tonic–clonic seizures after craniotomy than LEV had (OR 2.06×10^9, 95% CI 2.24 to not reached; p=0.008).

History of seizures before surgery was not associated with postsurgical seizures (OR 1.02; 95% CI 0.22 to 3.65; p=0.977). The lower rate of seizures in patients treated by LEV was also demonstrated in the patients who experienced no seizures prior to surgery. LEV was administrated to 52 of these patients and PHT to 58 patients. Among these patients, the incidence of seizures was 1.9% (1/53) in group L but 13.8% (8/58) in group P (p=0.034). The OR of the prophylactic effect of LEV compared with PHT was 8.16 (95% CI 1.42 to 154.19, p=0.015). Among the patients who exhibited seizures before craniotomy, the incidence of seizure was also lower in group L. In group L, no seizure was observed in 21 patients, whereas three of 15 (20%) patients in group P demonstrated seizures. The use of PHT had a higher risk of seizures compared with LEV (OR 9.66×10^7; 95% CI 1.78 to not reached, p=0.018). Although the number of patients whose seizure was intractable was small (5 in group L and 4 in group P), no seizure was observed among the patients in group L, while half of the patients in group P exhibited seizure within 1 week after surgery.

The influences of clinical and pathological factors on seizure prophylaxis are summarised in table 2.

Adverse events

Haematological toxicity was less frequent and mild but observed as follows: grade 3 liver dysfunction in three patients in group L (4.1%) and two patients in group P (2.7%) and grade 3 hyponatraemia in two patients in group P (2.7%). There was no significant difference in frequency of haematological toxicity between the two treatment groups, but grade 3 liver dysfunction required withdrawal of AED on postoperative day 6 in one patient who received PHT. In addition to this patient, PHT was withdrawn owing to grade 2 skin eruption in two patients on postoperative days 3 and 6, and grade 2 atrial fibrillation in two patients, both on postoperative day 1. PHT was withdrawn in five patients in group P (6.8%), although no patient in group L required withdrawal of LEV (p=0.058). After withdrawal of PHT, AEDs used before surgery were administered in two patients with a history of seizures (valproic acid and LEV in one patient each), but no further medication was administered to three patients without seizures. Fortunately, no seizure was observed after withdrawal of PHT in these five patients.

DISCUSSION

The incidence of perioperative seizures in patients with brain tumour without prior history varies. Lwu *et al*[19] have reported that only 3% (2/66) of patients with glioma developed seizure in the first postoperative week. Sughrue *et al*[20] also reported a low incidence of perioperative seizure (1.9%) after removal of meningiomas. In contrast, a higher incidence of seizures (7.5–31.7%) has also been reported.[21 15 22] The varied incidence of perioperative seizures was probably due to the use of retrospective data, which in general carry a bias, and proper incidence remains obscure. However, seizures can cause a worsening of neurological deficits and prolong hospitalisation after craniotomy, and prophylactic AEDs are routinely administered during and after surgery, despite incomplete evidence.

PHT is the most frequently selected AED for seizure prophylaxis in the perioperative period. In addition to the retrospective studies that have supported the prophylactic effect of PHT, North *et al*[3] have reported a significantly reduced incidence of perioperative seizures after craniotomy by PHT. However, that study included patients with a variety of diseases: aneurysm and head injury, as well as brain tumour, and the significance of the

Table 2 Influence of clinicopathological factors on perioperative seizures

	Risk group	OR	(95% CI)	p Values
Gender	Female	2.68	(0.81 to 9.49)	0.105
Age	≤60 year	1.03	(0.31 to 3.45)	0.961
Pathology (glioma/others)	Glioma	1.36	(0.41 to 4.79)	0.614
Location (frontal/others)	Frontal	2.51	0.76 to 8.88	0.130
Multiplicity (solitary/multiple)	Solitary	2.16	0.39 to 40.49	0.428
Maximum diameter (<40 mm/≥40 mm)	≥40 mm	1.44	0.43 to 4.82	0.549
History of seizure (yes/no)	Yes	1.02	022 to 3.65	0.977
(never or controlled/intractable)	Intractable	3.63	0.50 to 17.60	0.177
Anaesthesia (general/awake)	Awake	1.48	0.21 to 6.27	0.647
Duration of surgery	180 min≤	1.37	0.41 to 5.33	0.619
Extent of resection	GTR	1.06	0.30 to 4.98	0.932
Severe oedema after surgery	Yes	2.64	0.54 to 10.05	0.207
AED (LEV/PHT)	PHT	12.77	(2.39 to 236.71)	0.001

AED, antiepileptic drug; LEV, levetiracetam; PHT, phenytoin; GTR, gross total resection.

prophylactic effect of PHT was lost when patients with head trauma were excluded.[23] More recently, a prospective randomised trial also failed to show a significant effect of PHT on seizure prophylaxis in patients with intraparenchymal brain tumours.[24] These data raise a question about the use of PHT for seizure prophylaxis in the perioperative period. Furthermore, PHT is well known as a potent inducer of cytochrome P450 (CYP) 3A4.[25] Drug–drug interaction between PHT and agents metabolised by CYP3A4, which are frequently used during and after surgery for brain tumours,[26 27] has the potential to affect the treatment of tumours.

LEV is a broad-spectrum AED and is widely used for treatment of partial and generalised epilepsy. This agent is not metabolised by CYP in the liver and is renally excreted with minimal drug interaction, which makes it suitable for perioperative use. Recently, several investigators have tried to use this agent for seizure prophylaxis during and after craniotomy. Kern *et al*[28] reported a lower incidence of perioperative seizures in patients receiving LEV (2.5%), compared with PHT (4.5%), from a retrospective review of clinical records, even though this difference was not significant. From a retrospective review of patients at high risk for postoperative seizures, Gokhale *et al*[29] also demonstrated a low incidence of seizures in those treated with LEV. These data suggest the alternative choice of LEV instead of PHT for seizure prophylaxis during and after craniotomy. In the present study, we administered LEV suppositories, because intravenous LEV was not approved in Japan. The plasma concentration of LEV 2 h after insertion was within the range of previously reported data of Japanese patients who received the drug orally.[30] In our prospective randomised study, LEV showed a significantly lower incidence of perioperative seizures (1.4%) compared with PHT (15.1%). In addition to the significant effect of reducing the risk of seizures, LEV was safe and treatment was completed in all patients, although PHT was withdrawn because of adverse effects in 6.8% of the patients. Recently, Fuller *et al*[31] also compared the efficacy and safety of LEV with PHT in a randomised prospective study. In their study, the incidence of perioperative seizure was significantly lower in the LEV group (0/36) than in the PHT group (6/38, p=0.01), while the frequency of discontinuation because of adverse effects did not differ between LEV (1/36) and PHT (2/38). Although there was only a small number of patients (41/74) with brain tumours in their study group, their results were similar to ours and supported the efficacy and safety of LEV.

As described above, LEV was safe and effective for seizure prophylaxis, but our study still had some limitations. First, this single institutional study might have had a risk of temporal recruitment bias, even though the patient populations in the two treatment groups were generally well matched. Second, this study was carried out in a regional cancer centre, and the number of patients with benign tumours was low. Third, we administered 15–18 mg/kg FOS to patients in group P, because this dose was recommended by the manufacturer for prophylactic use. However, the plasma concentration of PHT was at the lower limit of the therapeutic range, and there remains the possibility that an insufficient dose caused the inadequate efficacy. The plasma concentration of PHT did not differ between patients who developed seizures and those who did not (average: 11.6±6.0 and 9.5±1.5 μg/mL, respectively, p=0.103). However, further evaluations with adequate plasma PHT concentration are required to draw conclusions regarding the prophylactic effect of PHT during and early after craniotomy. A fourth limitation was replacement of AEDs that had a sufficient effect on control of seizures before surgery with other AEDs: PHT or LEV. Furthermore, we stopped these AEDs on the day before surgery, and the timing of this replacement might have increased the risk of seizures. In this study, four patients taking LEV and two taking PHT prior to surgery were randomised to group P. Although none of these patients exhibited perioperative seizures, and change of AEDs did not affect the results, replacement of AEDs had the potential to increase the incidence of seizures, especially in group P.

We also tried to identify the risk factors for perioperative seizures. Age <2 years has been reported as a risk factor for seizures,[23] but our patients did not include children, and no clinical and pathological factors were correlated with the development of seizures. From these results, we could not predict the risk of seizures before surgery, and prophylactic LEV is recommended for its significant efficacy and safety.

As described above, prophylactic LEV in the perioperative period significantly reduced the risk of seizures, and it is recommended for treatment of patients with supratentorial tumours. The major limitation of this study was that it was a single-institution trial. We should be aware of the bias of limited recruitment of patients in single institutional studies on the significance of the seizure risk reduction for LEV. Multi-institutional double-blind studies are required to validate our results and confirm the efficacy of LEV for seizure prophylaxis during and after craniotomy in patients with brain tumours.

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