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Incidence and Management of Late Postsurgical Seizures in Clinical Practice

Klinik Uygulamada Cerrahi Sonrası Geç Havalelerin İnsidansı ve Takibi

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ABSTRACT

AIM: Seizures are a frequent complication in patients who undergo neurosurgery, and can complicate the post-operative course and deteriorate patients' quality of life. Evidence on the prophylactic anticonvulsant therapy after craniotomy is still lacking.

MATERIAL and METHODS: We undertook an observational longitudinal study following neurosurgical supratentorial interventions, to evaluate seizures onset or persistence, and differences in effectiveness between conventional and newer AEDs.

RESULTS: A total of 100 consecutive subjects were enrolled. Each patient underwent a neurosurgical treatment by craniotomy. Pre-operative seizures occurred in 33% patients, early seizures in 13%. Late seizures occurred in 46 patients. At baseline (1 month after surgery) and during follow up the main therapeutic regimen was monotherapy. At last follow up adjustment of antiepileptic regimen or AED dosage had rendered 27 subjects seizure free. People taking newer AEDs at baseline maintain the same antiepileptic regimen more often than patients taking conventional AEDs; late seizures tended to have a higher incidence in the latter group. Adverse events from baseline AEDs were reported by 17% of patients.

CONCLUSION: In this study population late postsurgical seizures had a remarkable occurrence. Newer AEDs were continued more often than conventional AEDs, with a better tolerability but no significant differences in late seizures incidence.

KEYWORDS: Post-operative seizures, Craniotomy, Antiepileptic drugs

ÖZ

AMAÇ: Havaleler beyin cerrahisi işlemleri yapılan hastalarda sık görülen bir komplikasyondur ve hastaların postoperatif seyrini komplike hale getirip yaşam kalitesini düşürebilirler. Kraniyotomi sonrasında profilaktik antikonvülsan tedaviyle ilgili bulgular halen az sayıdadır.

YÖNTEM ve GEREÇLER: Konvansiyonel ve yeni antiepileptik ilaçlar arasında etkinlik farklılıklarını ve havalelerin başlaması veya devam etmesini değerlendirmek için nöroşirürji supratentoriyal girişimlerini takip eden gözlemsel bir longitudinal çalışma yaptık.

BULGULAR: Çalışmaya arka arkaya toplam 100 hasta kaydedildi. Her hastada kraniyotomi şeklinde bir nöroşirürji tedavisi gerçekleştirildi. Preoperatif havaleler hastaların %33'ünde ve erken havaleler %13'ünde görüldü. Geç havaleler 46 hastada görüldü. Başlangıçta (cerrahiden 1 ay sonra) ve takip sırasında ana terapötik rejim monoterapiydi. Son takipte antiepileptik rejim veya antiepileptik ilaç dozunun ayarlanmasıyla 27 hastada havaleler ortadan kaybolmuştu. Başlangıçta daha yeni antiepileptik ilaçları alan kişilerde geleneksel antiepileptiklere göre daha sık olarak aynı antiepileptik rejime devam edildiği görüldü; geç havalelerin insidansı ikinci grupta daha yüksekti. Başlangıç antiepileptik ilaçlar nedeniyle advers olaylar hastaların %17'sinde bildirildi.

SONUÇ: Bu çalışma, popülasyonunda cerrahi sonrası geç havalelerin insidansı önemli ölçüdeydi. Daha yeni antiepileptik ilaçlar geleneksel antiepileptiklere göre daha sık devam edildi ve daha iyi tolere edildiler ama geç havale insidansında önemli bir fark yoktu.

ANAHTAR SÖZCÜKLER: Postoperatif havaleler, Kraniyotomi, Antiepileptik ilaçlar

INTRODUCTION

The actual incidence of epilepsy following neurosurgical interventions is poorly defined. Supratentorial surgery may be associated with the occurrence of early (i.e. within 1 week from procedure) or late seizures (i.e. beyond 1 week) (7,20). Early seizures are the acute symptomatic ones, depending on the immediate post-traumatic effect of the neurosurgical procedure (e.g. cerebral oedema, local inflammation, excitotoxic damage, oxidative stress, impairment of neuron metabolism) (5). Late postoperative seizures represent actual epilepsy and occur when acute symptomatic events are excluded (14). Onset of postoperative epilepsy has been widely investigated and several risk factors for late seizures have been described (e.g. primary disease, severity of surgical insult, pre-operative heraldic seizures occurrence) (14). Both early and late seizures negatively affect neurological outcome and patients' quality of life. Hence the possibility of postoperative seizure prophylaxis and therapy is more than desirable. The role of Anti Epileptic Drugs (AEDs) in risk reduction is debated (14,20). While antiepileptic treatment of seizures is mandatory, the advantage of prophylaxis with AEDs has not been clearly assessed. Many studies have focused on

first generation AEDs, especially phenytoin (PHT), with limited evidence on prophylactic or anti-epileptogenic effect (4,9,24). First generation AEDs can control early seizures but seem not to reduce incidence of late seizures. Studies with newer AEDs are scarce, but interest is rapidly increasing (13,16,22). The American Academy of Neurology recommends not to treat subjects with cerebral neoplasms and traumatic brain injury who have not had seizures beyond 1 week postoperatively or postinjury (4). However, there is considerable disparity between official guidelines and the management strategies pursued by neurologists and neurosurgeons (10,17,21).

The aim of this study was (i) to assess incidence of postoperative seizures in everyday neurosurgical practice, and (ii) to increase knowledge on newer AEDs efficacy and tolerability compared to first generation AEDs in postoperative seizure prevention and treatment.

MATERIAL and METHODS

A prospective longitudinal observational study was performed in a cohort of patients who consecutively underwent a neurosurgical procedure for supratentorial disorders. The study was carried out according to an open label design, in order to assess antiepileptic therapy and neurological outcome as in clinical practice. Patients could be included if they would undergo a neurosurgical procedure for supratentorial disorders other than epilepsy, and were aged above 18 years. Exclusion criteria were expected poor compliance, severe psychiatric illness and participation in an experimental trial.

Clinical assessments were undertaken by a neurologist trained in epileptology at 1 (*baseline*) and 6 months (*Follow Up Visit: FUV*) postoperatively, then every six months. Therapy was undertaken with *conventional* AEDs consisting of carbamazepine (CBZ), phenytoin (PHT), phenobarbitone (PB), valproic acid (VPA) the and *newer* AEDs consisting of lamotrigine (LTG), topiramate (TPM), oxcarbazepine (OXC), levetiracetam (LEV).

Data collected included demographics, primary disease, preoperative heraldic seizures, chemotherapy, radiotherapy, early seizures, late seizures, AEDs regimen, and adverse events (AEs).

Minimum follow up duration was established as 6 months. Primary endpoint was incidence of late seizures in the observed population. Secondary endpoints were comparison between conventional and newer AED monotherapy in terms of retention on the AED, late seizure control, and adverse events.

Summary statistics included medians with minimum and maximum values for continuous data and percentages for binary data. The Fisher exact test was used to compare groups in term of proportions. The study protocol was approved by the local ethics' committee. Patients had to sign an informed consent form to be enrolled in the trial. The study was conducted in two years time.

RESULTS

We included a total of 100 caucasian patients (52 males), with a median age of 52 years (range 21-86) in the study. Patients presented with glioma (n=27), meningioma (n=28), brain metastasis (n=6), spontaneous subarachnoid haemorrhage (ruptured brain aneurysm) (n=8), unruptured vascular malformation (n=18), subdural haematoma (n=4), parenchymal haemorrhage (n=2), and other neurosurgical disturbances (n=7) (Table I). Median follow up was 19 months (range 6-48) (Figure 1). During the course of the observation 15 patients had been treated by both chemotherapy and radiotherapy, 5 by chemotherapy only**.** Steroids were administered in 30 patients at some point of the observation. Incidence of pre-operative and early seizures is shown in Table II. During the cumulative observation, 46 patients (46%) presented late seizures (22 *de novo*, 9 preceded by either pre-operative and early seizures, 10 by early seizures only, 5 by pre-operative seizures only).

At baseline (1 month after surgery) 83 subjects were on monotherapy (43 on a conventional AED, 40 on a newer AED), 13 on polytherapy, and 4 were not receiving AEDs. At first FUV (6 months post-operatively) 79 subjects were on monotherapy (39 on conventional AEDs, 40 on newer AEDs), 16 on polytherapy, and 5 were not receiving AEDs. At last observation (end of follow up period) 76 subjects were on monotherapy (36 on a conventional AED, 40 on a newer AED), 18 on polytherapy, and 6 patients were not receiving AEDs. At last follow up visit change of antiepileptic regimen or AED dosage had rendered 27 subjects (52%) seizure free. Over the study period less people on conventional AED monotherapy maintained the same drug regimen than patients on newer AED monotherapy (81% vs. 95%, $p<0.10$) (Figure 2). The latter group had fewer late seizures (40%) than people on conventional AED monotherapy at baseline (42%), although differences were not statistically significant. People switched from baseline newer AED monotherapy to a different antiepileptic regimen for inefficacy (n=1), or inefficacy and AEs (n=1). The main reason for conventional AED monotherapy discontinuation was inefficacy (n=4), followed by inefficacy with adverse events (n=3) and AEs only (n=1). Doses of each AED during the follow up are shown in Table III. Adverse events from baseline AEDs were reported by 17% of patients, mostly associated with phenytoin (Table IV).

DISCUSSION

Management of antiepileptic therapy after a neurosurgical procedure is a widely debated issue, as evidence is quite limited, especially for the newer AEDs. We performed an observational longitudinal study to assess the incidence of postoperative epilepsy and to evaluate the role of conventional and newer AEDs in seizures control. The study cohort was constituted by patients consecutively referred to the epilepsy clinic following a neurosurgical intervention, with a balanced gender distribution and a wide age range. Pre-operative seizures attained 1/3 of study population and was comparable to frequency reported in other studies

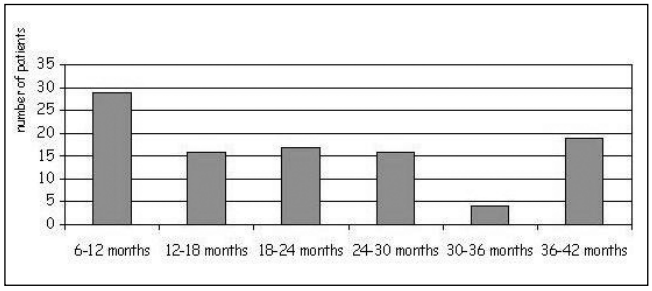

Figure 1: Follow up duration.

(2,12,16), while this study cohort had more early seizures than previous reports (11,12). Early seizures represent a well known risk factor for postsurgical epilepsy, as they correlate with the severity of the cerebral insult (14,20). In our study cohort incidence of late seizures (46% of study population) was quite elevated, occurring either in patients who had never experienced seizures before surgery and in subjects with pre-operative and early seizures. Cerebral neoplasms, especially gliomas, together with brain metastasis, were the most frequently observed primary diseases, and these epileptogenic lesions could have contributed to the high proportion of late occurring seizures.

Table I: Demographic and Clinical Data

		TOTAL (n=100)	Conventional AEDs monotherapy at baseline (n=44)	Newer AEDs monotherapy at baseline (n=40)	Polytherapy at baseline (n=12)	No therapy at baseline (n=4)
AGE yrs, mean (range)		51.9 (21-86)	56.6 (22-86)	46.4 (21-68)	50.1 (33-76)	59.0 (45-66)
SEX, male		52%	45.5%	57.5%	58.3%	50.0%
PATHOLOGY (n)						
Gliomas						
	Grade III-IV	16	6	6	4	0
	Grade I-II	11	3	3	4	1
Meningiomas		28	14	12	1	1
Cerebral metastasis		6	2	2	1	1
Spontaneous SAH		8	5	2	1	0
AVMs		3	2	1	0	0
Cerebral aneurysms		10	4	5	1	0
Cavernous angiomas		4	1	3	0	0
Artero-venous fistula		1	0	0	0	1
Subdural haematomas		4	2	2	0	0
Parenchymal haemorrage		2	1	0	1	0
Contusive trauma		1	0	1	0	0
Congenital hydrocephalus		1	0	1	0	0
Foreign matter inclusion		1	0	1	0	0
Undetermined lesion		4	2	2	0	0
Chemotherapy (n)		20	7	7	6	0
Radiotherapy (n)		15	5	6	4	0

AVMs= *Arteriovenous Malformations,* ***SAH =*** *Spontaneous Subarachnoidal Hemorrhage.*

Table II: Seizures Occurrence at Baseline

PATIENTS	TOTAL (n=100)	CONVENTIONAL AEDs monotherapy at baseline (n=44)	NEWER AEDs monotherapy at baseline (n=40)	Polytherapy at baseline (n=12)	No therapy at baseline (n=4)
Pre-operative seizures (n)	33	13	14	5	1
Early seizures (n)	13	6	4	3	0

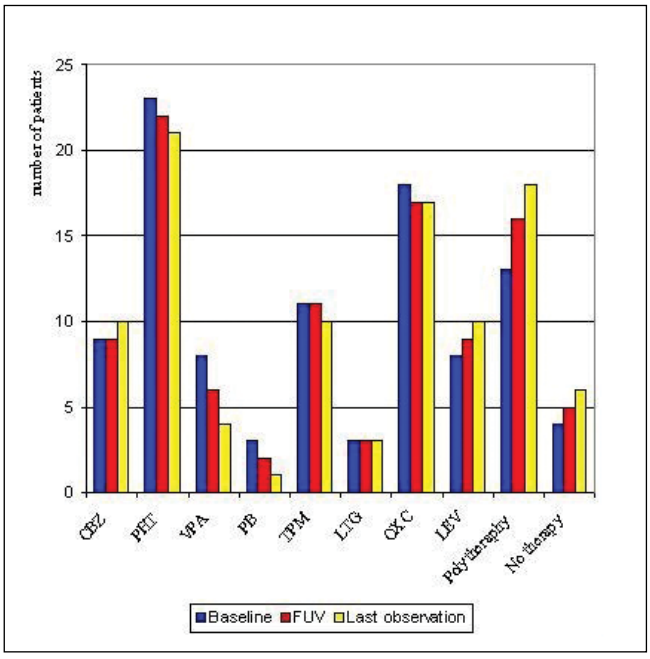

Figure 2: Antiepileptic therapy along the course of the observation.

Table III: Dose of Antiepileptic Drugs During Cumulative Follow up

	most frequent dose	*maximum dose*	*minimum dose*
PB	100 mg/day	100 mg/day	100 mg/day
PHT	200 mg/day	300 mg/day	100 mg/day
VPA	700 mg/day	1000 mg/day	500 mg/day
CBZ	1200 mg/day	1400 mg/day	800 mg/day
OXC	1200 mg/day	2100 mg/day	600 mg/day
TPM	200 mg/day	400 mg/day	50 mg/day
LTG	200 mg/day	300 mg/day	150 mg/day
LEV	2000 mg/day	3000 mg/day	1000 mg/day

The large majority of patients were receiving antiepileptic treatment since neurosurgical procedure, mainly as monotherapy, with a balanced proportion of conventional and newer AEDs. Despite the early initiation of drug treatment, AEDs seemed not to protect subjects from late seizures occurrence. In fact, almost half of the study population developed late seizures, with a remarkable amount of *de novo* seizures. However, over the study period adjustment of antiepileptic regimen, either drug change or modifications of daily doses, rendered seizure free 27 out of 46 patients.

In the study cohort initial treatment with newer AEDs was maintained more often than conventional AEDs. We may speculate that retention on the baseline therapy could have reflected a combination of better efficacy and tolerability. In fact, newer AEDs tended to be associated with fewer late seizures and a better tolerability than established anticonvulsants, although differences were not statistically significant. Adverse events occurred more often following PHT intake as initial monotherapy regimen. It is noteworthy to consider that a consistent proportion of our population was treated with chemo/radiotherapy and steroids. Drug interactions are much more frequent with older than newer AEDs (8,18). Furthermore, enzyme-inducing AEDs (PHT, CBZ, PB) increase the clearance of corticosteroids and reduce the clinical efficacy of some anticancer agents (15,26). These effects could result at least in part in a poor therapeutic response and drug discontinuation of older AEDs, as reported for PHT (19).

Seizures occurrence and management is an outstanding issue in the care of people with a neurosurgical disorder. Post-operative epilepsy may hamper an optimal neurological outcome and quality of life. Seizures can also have a negative prognostic value, especially in brain tumor surgery. Persistent seizures after macroscopically complete tumor resection could signal an acceleration in tumor growth or indicate an anaplastic transformation (23). Further studies are needed to better define risk factors for post-operative epilepsy and late seizures prognostic value. Role of antiepileptic therapy in seizure prevention should be explored on an evidence based

Table IV: Adverse Events During Cumulative Follow up (n)

	OXC	*TPM*	*LEV*	*LTG*	*PHT*	*PB*	*VPA*	*CBZ*
Rash	0	0	0	0	2	0	0	0
Liver toxicity	0	0	0	0	4	0	0	0
Paresthesias	0	1	0	0	0	0	0	0
Weight gain	0	0	0	0	0	0	1	0
Sedation	1	1	1	0	0	0	0	0
Gengival hypertrophy	0	0	0	0	2	0	0	0
Periarthritis	0	0	0	0	0	1	0	0
Hyponatremia	1	0	0	0	0	0	0	0
Dizziness	0	0	0	0	1	0	0	0
Insomnia	0	0	0	1	0	0	0	0

All events were reported on monotherapy (except 1 CBZ add on and 1 PHT add on).

approach. Our study was aimed at assessing the therapeutic potential of AEDs in late emerging postoperative seizures, as placebo-controlled study and clear cut evidence on this issue are still lacking (25). International guidelines suggest not to use AEDs as seizure prevention in postsurgical patients (4,17), but in many cases routine use of anticonvulsant drugs remains the prevailing practice (6,10,11,17,21,27). Eventually, the large majority of studies have focused on the use of conventional AEDs in neurosurgical patients. Newer AEDs should be further investigated for their potential advantages, including the availability of intravenous formulation that could offer a realistic alternative to traditional perioperative phenytoin i.v. therapy (1,3).

DISCLOSURE

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Abbreviations used in this paper:

AED: Antiepileptic Drug, **AVMs:** Arteriovenous Malformations, **CBZ:** Carbamazepine, **FUV:** Follow up Visit, **LEV:** Levetiracetam, **LTG:** Lamotrigine, **OXC:** Oxcarbazepine, **PB:** Phenobarbital, **PHT:** Phenytoin, **SAH:** Spontaneous Subarachnoidal Hemorrhage, **TPM:** Topiramate, **VPA:** Valproic acid

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